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INFECTIVE HEPATITIS: ITS INCIDENCE AND ITS SEQUELÆ.[1]

By C. E. MARSHALL,[2]

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The winter coming on and sickness growing
Upon our soldiers, we will retire to Calais.

(King Henry V, III, 3, 56.)

INFECTIOUS HEPATITIS is a subacute contagious disease characterized by focal necrosis of the liver, with or without jaundice, and by the presence of a virus in an infective state in the blood. It occurs in an epidemic and a sporadic form, and complete recovery is the rule.

It is a disease of great antiquity; Hippocrates (Adams, 1849) recognized it two and a half thousand years ago, when he recorded the case of his patient Hermocrates who lived by the New Wall, a district notoriously associated with contagious illnesses. Hermocrates was seized one day with fever, headache and pains in the back accompanied by loss of appetite. On the sixth day of his illness he developed jaundice and his urine was dark and red. On the fourteenth day he appeared better and the fever had gone, although the jaundice still persisted; but on the twenty-fourth day he suffered a relapse and became comatose, and he finally died from acute liver failure on the twenty-seventh day of his illness.

Virus diseases are subject to change. Old ones disappear and new ones are recognized; this is the changing pattern of disease (Engel, 1956); but infectious hepatitis has persisted since the days of ancient Greece, and it has followed all the major military expeditions through the ages like a shadow. In spite of its tenacious hold on civilization, however, infectious hepatitis, like epidemic influenza, displays varying degrees of virulence in different epidemics. This feature in all probability has been the cause of the great differences of opinion concerning the incidence and seriousness of its sequelæ and the need or not for prolonged physical rest during the convalescent stage of the illness. At the present time there is every indication that we are experiencing a phase of increased virulence of the disease (Figure III).

In recent times infectious hepatitis has supplanted dysentery and typhus as a cause of morbidity amongst military personnel. It accompanied Napoleon to Africa; it was present amongst troops during the American Civil War, at the Boer War, and in both World Wars (Havens, 1947). A lack of understanding of the underlying pathology and causes of the different varieties of jaundice which we now recognize led to confusion regarding prognosis and treatment, a confusion which was enhanced rather than

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clarified by the isolation of the *Leptospira icterohæmorrhagiæ* in 1915. After this important discovery, most cases of infectious hepatitis came to be regarded as spirochætal jaundice (Paul, 1946), although, as early as 1912, the two diseases were recognized as being separate entities, and it was then also realized that acute yellow atrophy could develop as a sequel to infectious hepatitis (Cockayne, 1912). In spite of this, innumerable cases of infectious hepatitis which occurred at Gallipoli were thought to be caused by an icterogenic strain of salmonella, from the fact that cultures of blood from soldiers suffering from jaundice grew paratyphoid organisms in a large number of instances (Sarrailhé and Clunet, 1916). It is not surprising that this misconception should have arisen, since the modes of infection of the two diseases, infectious hepatitis and paratyphoid fever, are presumably the same. During World War II tens of thousands of cases occurred amongst troops of all nations in various parts of the world. A great deal has been learnt about the disease since then. First, the relationship of the underlying pathological changes in the liver to the clinical phase of the disease has been clarified—knowledge gained from improvement in the techniques of needle biopsy. Secondly, valuable information regarding the ætiology and transmission of the disease has been obtained from experiments in human volunteers. Nevertheless, much yet remains to be learnt, principally in regard to the more accurate diagnosis of jaundice in general and of non-icteric hepatitis in particular. The science of bacteriology can give little aid at present, and the next major advances envisaged will be the development of a reliable serological test and the discovery of a consistent means of propagating the virus outside the human body. Reports of the successful tissue cultivation of the virus and of the preparation of reliable antigens await confirmation, and such confirmation can at present be obtained only by the use of human volunteers. This fact is one of the greatest bars to rapid progress; but once this obstacle has been overcome there is no reason to suppose that the incidence of infectious hepatitis should not be reduced eventually to the insignificant numbers which are now considered usual for typhoid fever in civilized communities.

Classification and Ætiology.

No successful attempt has yet been made to transmit the disease to animals, even including chimpanzees, and the currently-held view of the virus ætiology of infectious hepatitis is based upon the transmission of the disease to human volunteers by a filtrable agent obtained from the fæces and blood of patients, and upon the consistent failure to identify any causative bacteria with the disease (Havens, 1947).

At least two infective agents are involved which, although related by a number of similar physical properties, differ from each other both immunologically and epidemiologically. For example, both viruses are extremely small and can pass the finest filters, and both are unusually resistant to heat. In the dried or frozen state they may remain infective for many months. They differ from each other principally in their modes of transmission and in their incubation periods.

These two agents have been conveniently termed "virus IH" and "virus SH" (sometimes referred to as "virus A" and "virus B" respectively). "Virus IH" is responsible for the common sporadic and epidemic forms of infectious hepatitis, while "virus SH" produces the parenterally-transmitted disease known as homologous serum hepatitis. The main distinguishing features of these two syndromes are summarized in Table I.

Since the differentiation of the two conditions is based upon these different clinical and epidemiological characteristics and not upon identification of the ætiological agent, it sometimes happens that difficulty is experienced in deciding to which category a particular case belongs. Undoubtedly some cases of homologous serum hepatitis actually represent the artificial transmission of infectious hepatitis by the parenteral route, and when this occurs the incubation period will tend to be much shorter. Such cases, in which the mode of infection cannot be accurately determined, are often classified under the more general term of "viral hepatitis".

Epidemiology.

Age and Sex Incidence.

Since military personnel form a selected group as regards both age and sex, a more accurate idea of the age incidence of infectious hepatitis can be obtained from a study of civilian epidemics rather than military epidemics. This is not to deny that the age incidence in soldiers displays the same trend as in civilians.

All are agreed that infectious hepatitis is a disease of children and young adults, and that its incidence declines sharply after the age of thirty years. In one British

TABLE I.

The Main Distinguishing Features of Infectious Hepatitis and Homologous Serum Hepatitis (from Neefe, 1949).

Infectious Hepatitis.	Homologous Serum Hepatitis.
Contagious.	Not contagious.
Incubation period two to six weeks.	Incubation period six to twenty-four weeks.
Virus present in the fæces and blood.	Virus present in the blood only.
Experimentally transmissible by mouth (using infectious fæces and serum).	Not transmissible by mouth (using infectious fæces and serum).
Transmissible by parenteral injection (using infectious serum).	Transmissible only by parenteral injection (using infectious serum).
One attack confers immunity to "IH" but not to "SH".	One attack confers some immunity to "SH", but not to "IH".
May be prevented by the prophylactic injection of human gamma globulin.	Is not prevented by the injection of human gamma globulin.
Onset abrupt with fever and chills.	Onset insidious with little or no fever.
Abnormal results to liver function tests develop after symptoms appear.	Abnormal results to liver function tests develop before symptoms appear.
Commonest in autumn and winter (dependent on epidemiology).	Occurs all the year round (dependent upon chance inoculation).
Affects children and young adults.	Affects persons of any age subjected to injections.
Skin test[1] with "virus IH" gives positive result.	Skin test with "virus IH" gives negative result.
Virus cannot be recovered from the blood during the incubation period.	Virus can be recovered from the blood during the incubation period.

[1] Awaits confirmation.

civilian epidemic (Ford, 1943), four-fifths of the victims were children below the age of fifteen years, and in one comparable American epidemic (Feemster and Hardy, 1946) slightly less than half of the patients were below the age of fourteen years and two-thirds were below the age of twenty years. A preponderance of juvenile cases was also observed in the outbreaks which occurred in Germany prior to World War II (Figure I) (Paul and Gardner, 1950).

Babies are by no means immune, and non-icteric hepatitis is known to occur in endemic form among them ("Current Comment", 1955). Some of these infants display symptoms for a prolonged period of time, with progressive liver damage which may not become manifest until childhood. Such is the case especially in institutions. The infants have been found to harbour the virus in their fæces for many months, so that they can act as an unrecognized reservoir of infection from which their young adult attendants are able to acquire the characteristic disease with jaundice.

The age incidence of infectious hepatitis is thus similar to that which was once considered usual for poliomyelitis, and it is suggested that the decreased incidence which is found in the older age groups is due to the development of an active immunity against the virus. It might further be assumed that this immunity was due to the ingestion of submorbid doses of the infectious agent from time to time, and epidemics of hepatitis would therefore be expected to attack a populace either when the virulence

of the agent became enhanced, or when the antibody titre of a particular group of individuals was low.

As a rule, there is no significant difference in incidence between the sexes; but an epidemic which was reported from Denmark in 1947 constitutes the exception to this rule (Alsted, 1947). This epidemic was most unusual, not only as regards the age and sex incidence of the disease, but also in respect of its severity. The outbreak was confined almost exclusively to women over the age of forty-five years, and exactly 50% of them died. For this reason it was described as an epidemic of "malignant hepatitis". The pathological changes in the liver were those of active and rapidly progressing portal cirrhosis.

The age and sex incidence of homologous serum hepatitis, on the other hand, is solely dependent upon the category of patient exposed to parenteral inoculation with blood or its products. The disease thus occurs in the older age groups of both sexes who are given therapeutic transfusions for diseases peculiar to their group, and in younger persons who are exposed through the prophylactic administration of gamma globulin for various virus diseases. The younger group is unlikely to become infected by vaccination or diagnostic procedures which do not involve the administration of human serum in these days of enlightenment; but infection has resulted from tattooing performed by persons ignorant of the precautions necessary to ensure adequate sterilization of their equipment (Case II).

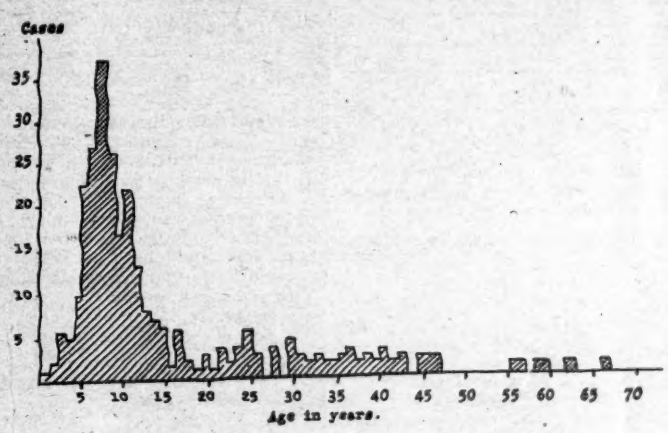


FIGURE 1.

Age incidence of infectious hepatitis in a German civilian epidemic prior to World War II. (From Paul and Gardner, 1950.)

Racial and Geographical Incidence.

There is no evidence to show that any particular race is more susceptible to infectious hepatitis than another, although the liability to exposure may vary in different racial and social groups. The efficiency of sewage disposal is important in this respect, since the contamination of water supplies by infected material has been reported. The attitude to cleanliness of certain groups will also affect the incidence to some extent, although the high degree of resistance of the organism makes control by this means difficult.

Because of the higher incidence of syphilis amongst them, Negroes in the United States were at one time more frequently exposed to the risk of homologous serum hepatitis during arsenotherapy; but "needle jaundice", resulting from the perfunctory sterilization of syringes, should now be only a matter of historical interest.

There is no question that infectious hepatitis has a world-wide distribution.

Numerical Incidence.

Infectious hepatitis is a notifiable disease only in a very few countries, principally in Sweden, Denmark, Australia and Canada, and in some of the United States. Even in these countries the figures depend upon the accuracy of diagnosis, and the true incidence is believed to be at least 50% to 75% greater than the number of cases notified. This discrepancy arises from the difficulty in recognizing mild and non-icteric cases, which are often diagnosed as minor gastro-intestinal disturbances (Case III). During epidemics of infectious hepatitis, clinicians are more alert to this difficulty than at other times, and so the number of cases notified during an epidemic is likely to be more accurate than at other times. Notwithstanding this accepted inaccuracy in notification, the figures reported are invaluable in pointing the seasonal incidence and general epidemiological trend of the disease from year to year.

Table II compares the incidence of infectious hepatitis for the year 1955 in the four countries, Australia, Canada, Sweden and Denmark. These figures show that there is quite a wide difference in apparent incidence for countries having similar economic backgrounds. This is partly accounted for by differences in the accuracy of notification, but mostly it is due to the natural epidemiological habit of the disease. Its morbidity varies greatly. For instance, the disease may give rise to sporadic cases, or it may assume an explosive epidemic form in which 50% of the exposed population becomes infected (Wilson and Miles, 1955). Between these extremes there is the pattern in which small epidemics maintain the incidence at a more or less constant level. Abortive and non-icteric cases, whilst escaping notification, are a source of continued infection.

Figure II illustrates the numerical incidence of the disease in Denmark, Sweden, Canada and Australia during the decade 1946-1955.

Canada shows a low over-all incidence with a slight recent rise.

Australian figures are incomplete, since only in Western Australia was the disease notifiable before 1952. Even today it is still not notifiable in the State of Queensland.

Denmark and Sweden both report a progressive and conspicuous fall in the number of cases notified during the decade. The decline is not due to any revolutionary changes in public health measures, but is due to the usual cyclical waxing and waning of the disease, and to an increased immunity of the population such as is found in other epidemic diseases. For instance, the low incidence for Denmark in 1953 is not unique, since an even lower trough occurred in the period 1936-1940, and this was preceded by a peak in 1932.

In 1949, in Sweden, the Medical Board issued recommendations to minimize the transmission of homologous serum hepatitis (Olin, 1956), which, however, can account for only a small part of the great decrease noted at this time.

Table III gives the highest incidence rate in each of the three countries in which the disease was notifiable during the period 1944-1955, and the year in which that rate was recorded.

Seasonal Incidence.

In Europe, the seasonal incidence of acute infectious hepatitis has always been greatest in the autumn and early winter months (Figure III). This does not necessarily indicate that the disease is ordinarily spread by droplet infection as has been suggested (Gauld, 1946). At least one other virus disease (cat-scratch fever) displays a very similar seasonal incidence (Marshall, 1956), and its mode of transmission is quite different from that of either infectious hepatitis or respiratory disease. Since infectious hepatitis is a disease acquired by close personal contact, it is possible that the congregation of people indoors during the winter may account for the seasonal incidence found in Europe.

In Australia, during 1955-1956, the incidence did not follow the usual European pattern (Figure IV). Here the peak was reached during the height of the summer and was of major epidemic proportions. By analogy with other enteric infections, such a higher incidence in the summertime, when more cold and uncooked food is consumed, is rather to be expected. Also, in the milder

TABLE II.

Incidence of Infectious Hepatitis Notified in Four Countries During the Twelve-Month Period January 1, 1955, to December 31, 1955.

Country.	Population.	Cases of IH Notified in 1955.	Rate per 10,000 of Population.
Australia	7,962,608[1]	7264[1]	9·1
Canada	15,573,000	3861	2·5
Sweden	7,234,664	1038	1·4
Denmark	4,424,000	5223	11·8

[1] Excluding Queensland.

Australian climate the tendency to spend much time inside closed and crowded buildings is not much greater in the winter than in the summer.

Homologous serum hepatitis, of course, shows no seasonal incidence.

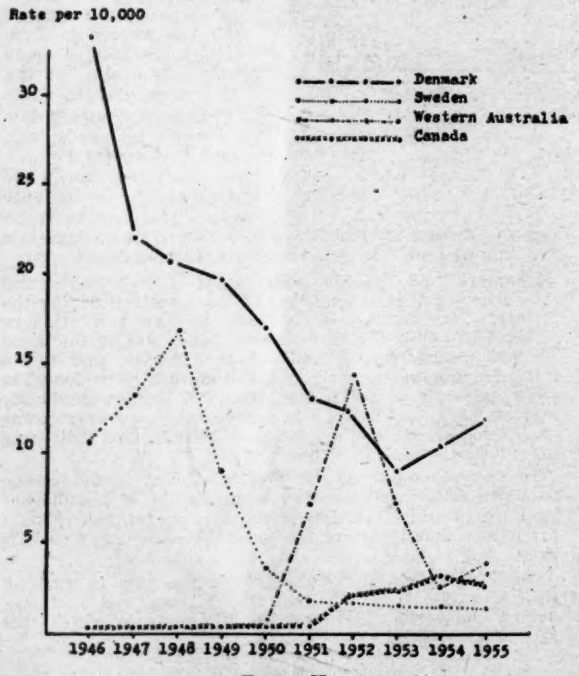


FIGURE II.

Incidence of infectious hepatitis in four countries for the decade 1946-1955 inclusive.

Sequelæ.

Failure to recover from acute infectious hepatitis is exceptional. In spite of the high morbidity of the disease, the mortality rate is less than 0·5% (Paul, 1946; Feemster and Hardy, 1946). This is remarkable in view of the severe damage which is to be seen on histological examination during the acute stage (Figure V). These changes consist of liver cell necrosis, especially in the centres of the lobules, and inflammatory cell infiltration, which is most marked in the portal tracts. All degrees of liver cell autolysis occur, from a strictly centrilobular zonal necrosis in the milder cases to a diffuse lesion which affects the whole lobule in the more severe cases. As a result of necrosis of the liver cell columns, the reticulin framework of the lobule collapses but is not destroyed, so

TABLE III.

The Highest Incidence Rate in Each of Three Countries During the Period 1944–1945, and the Year in which the Highest Rate was Recorded.

Country.	Rate per 10,000 of Population.	Year.
Canada	3·0	1954
Sweden	16·8	1948
Denmark	38·0	1944

that the liver cells can regenerate without hindrance along these reticulin "guide rails" again. In the milder cases of infectious hepatitis, or in those cases in which recovery is taking place, the inflammatory cell infiltration of the portal tracts is the most conspicuous feature, whereas in the severer cases hepatocellular necrosis is more pronounced and the cellular reaction more widespread (Dible, McMichael and Sherlock, 1943). After clinical recovery is complete, the portal tracts sometimes remain distended with lymphocytes and histiocytes for many months. There

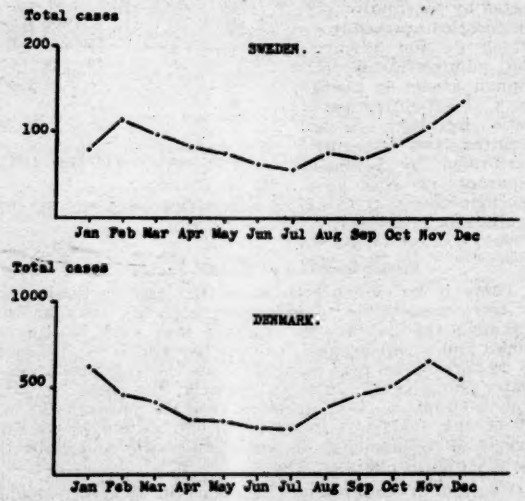


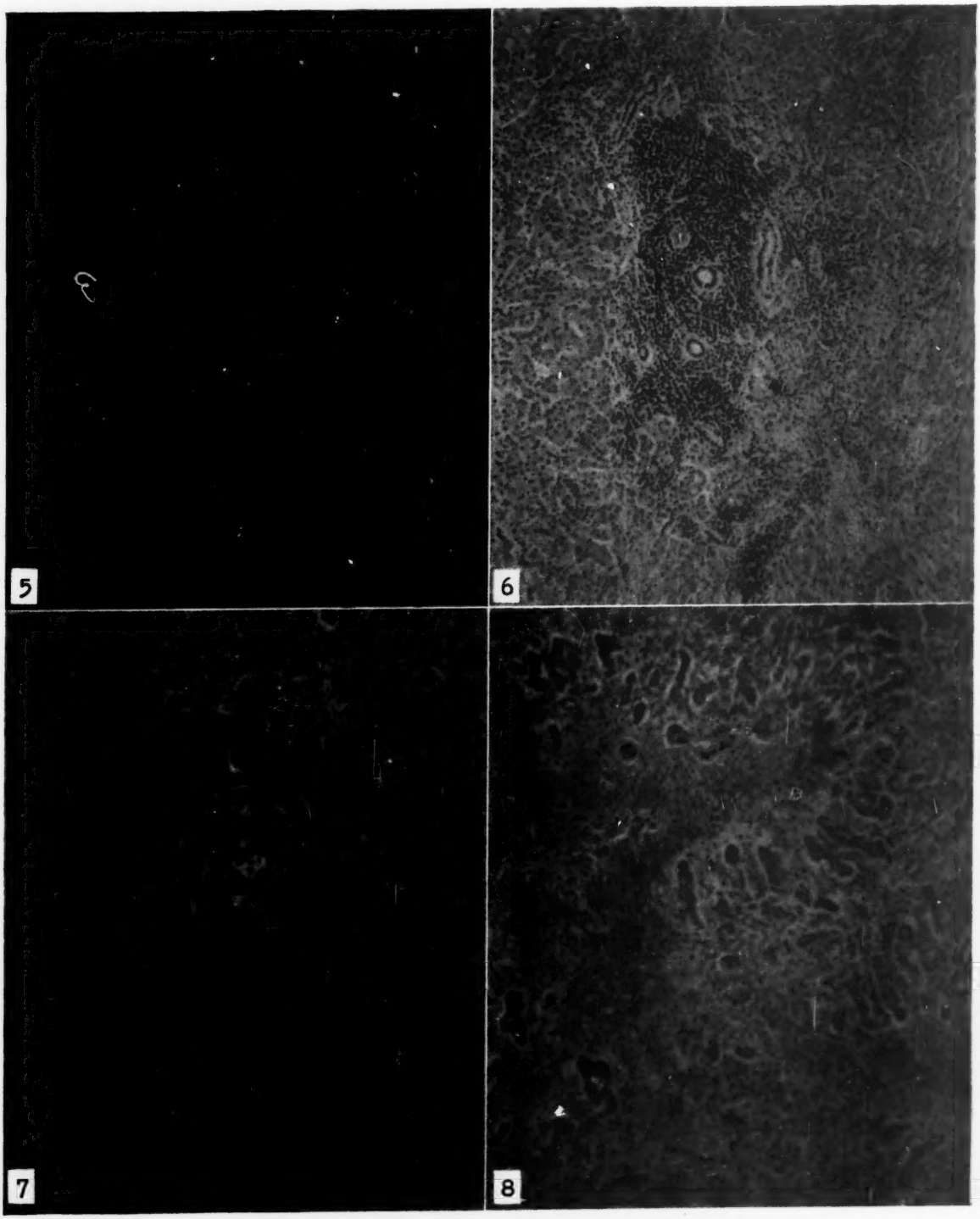
FIGURE III.

Seasonal incidence of infectious hepatitis in Sweden and Denmark, 1955.

is often, too, an increased amount of collagen around the triads, so that the condition is referred to as "persistent portal scarring" (Figure VI). True cirrhosis is very rare, and this residual fibrotic scarring disappears completely with time.

Complete recovery from acute infectious hepatitis takes place within four months and usually within a week or two. The return of the appetite and a progressive fall in the serum bilirubin level are valuable indications of anatomical liver recovery. The serum bilirubin reaches its highest level during the first week of the disease, the actual figure depending upon the extent of hepatocellular damage. After the first week there is a gradual fall in the serum bilirubin level, which commonly drops to two milligrammes per 100 millilitres within three weeks. The patient is usually advised to remain at rest until the

ILLUSTRATIONS TO THE ARTICLE BY C. E. MARSHALL.



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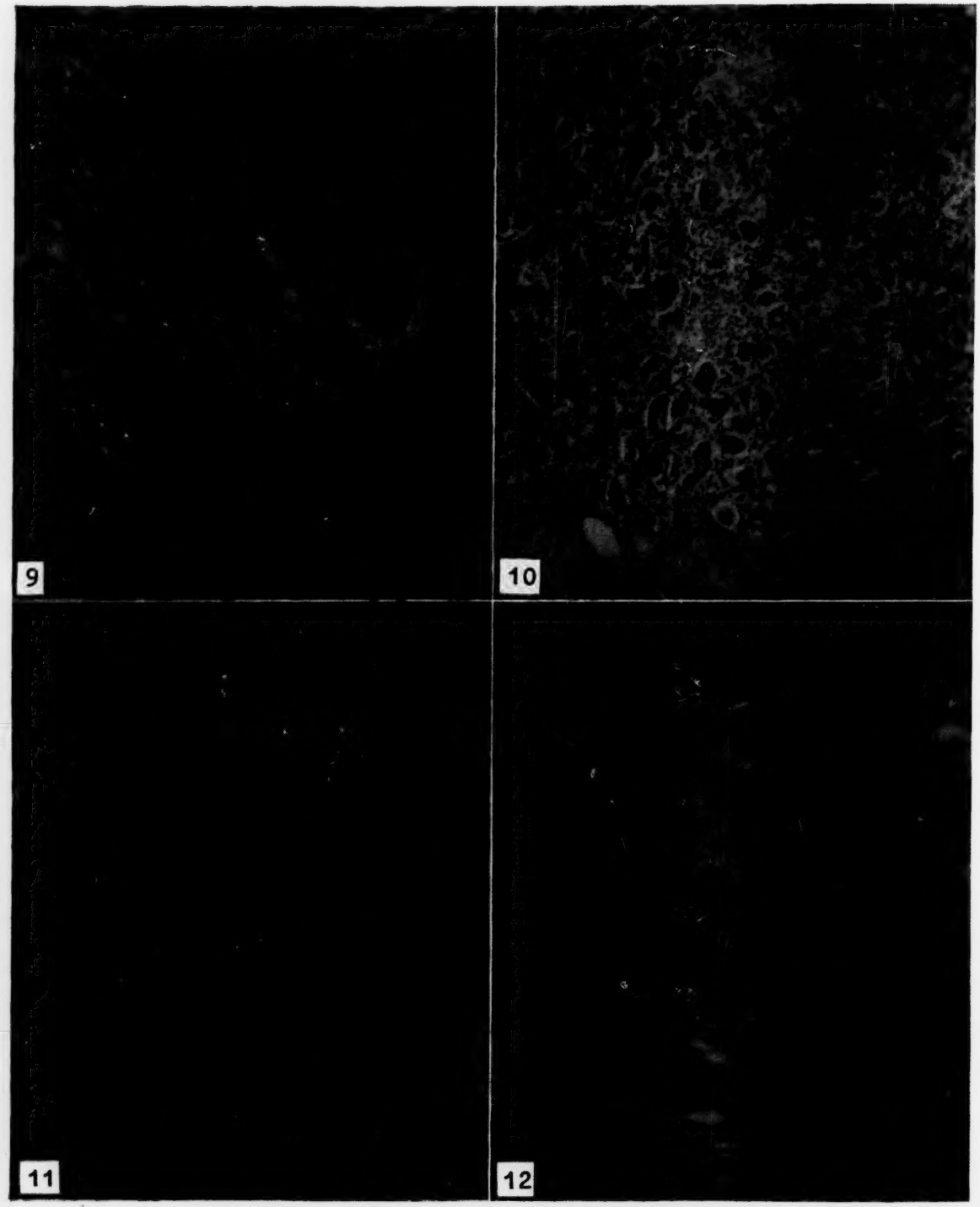

serum bilirubin concentration falls to one milligramme per 100 millilitres. On recovery, the total serum proteins do not increase significantly, but there is an alteration in the albumin-globulin ratio, the albumin level rising and producing a relative fall in the globulin (Sherlock, 1946).

Post-Hepatitis Syndrome.

During convalescence, symptoms of weakness, loss of energy and fatigability are common, but soon subside. In the post-hepatitis syndrome (Caravati, 1944), these vague symptoms of ill-health persist for months or years after all histological and biochemical evidence of liver damage has disappeared. The syndrome is thus thought to be psychosomatic in origin, but it is always specifically related to a preceding attack of acute hepatitis. Doctors and nurses, who have some knowledge of the possible serious sequelæ of infectious hepatitis, are prone to develop symptoms. These are fatigue, loss of weight, anorexia, abdominal discomfort and emotional instability. There is often an

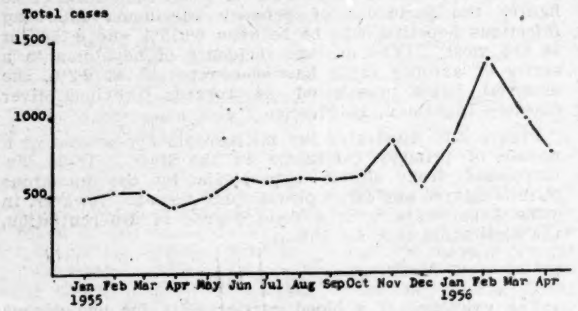

FIGURE IV.
Seasonal incidence of infectious hepatitis in Australia, 1955-1956.

aversion to fatty food with fussiness over diet. From a structural, secretory and motor viewpoint, the hepatobiliary and gastro-intestinal tracts have been found to be normal in all cases.

It must be emphasized that aspiration liver biopsy is the most valuable procedure for distinguishing organic from functional liver disorders, and that clinical and biochemical tests cannot always be relied on to do this (Sherlock and Walshe, 1946). Even when there are abnormal biochemical findings in a person who has suffered from infectious hepatitis, a liver biopsy may disclose some other condition responsible for the impaired liver function, such as an infectious granuloma, rather than cirrhosis (Neefe *et alii*, 1943).

Aspiration liver biopsy is a relatively safe procedure, having a reported mortality of 0·17% (Sherlock, 1955). After biopsy, if the liver is histologically normal, the reassurance which can be given is of great benefit to the patient. In the very occasional case, persistent portal scarring has been found on biopsy (Sherlock and Walsh, 1946; Neefe, 1946; Armas-Cruz, 1946); but the infrequency with which cirrhosis follows this testifies to its harmlessness as a prognostic finding.

The most useful biochemical tests, when the post-hepatitis syndrome is suspected, are the bromsulphalein retention test (using five milligrammes of dye per kilogram body weight and taking five minute and thirty minute samples of blood), and the determination of the urinobilinogen content of the urine and the serum bilirubin level. The abnormal retention of bromsulphalein often occurs before the serum bilirubin level is raised, early in acute hepatitis, and sometimes remains the only evidence of disturbed liver function during convalescence when the serum bilirubin level is again normal (Havens, 1950). In organic disease, however, the serum bilirubin level and urinary urinobilinogen level will also frequently show a slight but constant elevation (Swift *et alii*, 1950). (For the routine study of any jaundiced patient, the most valuable additional tests are the serum alkaline phosphatase and the differential protein estimations repeated at weekly intervals—Sherlock, 1946.)

Fatal Subacute Infectious Hepatitis.

In fatal subacute infectious hepatitis, although the parenchymal damage may be severe, the architectural disorganization is much less apparent than in either acute yellow atrophy or cirrhosis. In acute yellow atrophy death occurs with fulminating massive necrosis during the acute stage of hepatitis. In subacute infectious hepatitis recovery is delayed if zonal necrosis actively continues, and death may then complete the story some four to ten weeks later (Mallory, 1947).

CASE I.—This is an example of fatal subacute infectious hepatitis. A female patient, aged 42 years, was first examined six weeks before death, with the complaint of severe pain in the right shoulder and the back, and anorexia. Marked stomatitis and gingivitis were present. Two weeks later she complained of profuse uterine bleeding, which continued intermittently until her death. (Although thrombocytopenia has been reported in infectious hepatitis, in this case the menorrhagia was thought to have been caused by inadequate production of prothrombin by the liver. In yellow fever the prothrombin deficiency may be so marked that hæmoglobinuric nephrosis results—Elton *et alii*, 1955.) Two weeks before death she was again examined and complained of persistent anorexia, weight loss and weakness. She had no jaundice at any time, but was extremely pale from blood loss, which continued despite numerous transfusions. At the time of her death there were marked pallor, wasting, air hunger and exsanguination. It is possible that recovery might have occurred had it not been for the protracted bleeding. Hepatitis had not been suspected before death.

At autopsy numerous cutaneous petechiæ were present, and the body was markedly emaciated and pale. Nothing else unusual was noted excepting for enlargement of the liver and spleen (weights not recorded).

Figure VII illustrates the microscopic appearance of the liver.

Acute Yellow Atrophy (Massive Necrosis).

The mortality rate during the active stage of acute infectious hepatitis is less than 0·5%. In the epidemics which have occurred during World War II, and in the outbreak of homologous serum hepatitis which followed the inoculation of United States troops with yellow fever vaccine in 1942, the mortality rate was estimated to be in the vicinity of 0·2% (Neefe, 1954). Because of the difficulty in diagnosing mild, non-icteric cases, this figure may be too high. More recently there seems to have been an increase in the virulence and mortality of the disease, particularly of homologous serum hepatitis.

The number of fatal cases in any epidemic depends upon the virulence of the particular strain of virus causing the epidemic, upon the specific and general resistance of the patient and possibly upon the size of the viral dose and the management of the patient. It is impossible to predict which case will have a fatal outcome from the severity of symptoms or the degree of jaundice during the acute stage. In cases which appear mild and which are running a normal course, acute yellow atrophy may develop with disturbing suddenness.

Although many drugs and chemical poisons are known to produce liver cell necrosis, acute yellow atrophy has long been recognized as an important sequel of infectious hepatitis (Cockayne, 1912). Case II provides an example of fatal acute yellow atrophy following the inoculation of the virus of homologous serum hepatitis.

CASE II.—A naval dockyard clerk, aged 18 years, visited a tattoo shop and had both forearms tattooed. Three and a half months later he developed jaundice, pain in the abdomen and nausea. He remained in bed for two weeks, but the abdominal pain increased in severity and was accompanied by vomiting. He was admitted to hospital in a delirious state with marked jaundice. He died two days later in hepatic coma.

On investigation, his liver and spleen were not palpable. The urine contained bile and sugar (perhaps because of failure to metabolize glucose solution given intravenously). The following results to biochemical tests were obtained. The

prothrombin time was 55 seconds (control 13 seconds). The thymol turbidity was 16 units, and the thymol flocculation test produced a "+" result. The result of the cephalin cholesterol flocculation test was "++++". The serum non-protein nitrogen content was 25 milligrammes per 100 millilitres, the serum alkaline phosphatase content was 4 King-Armstrong units and the serum bilirubin content was 45 milligrammes per 100 millilitres.

At autopsy, jaundice was present and there were numerous petechial hæmorrhages of the skin and serous surfaces. The liver was reduced in size and mottled yellowish-brown. The spleen was enlarged (320 grammes), soft and reddish-brown in colour. The stomach contained altered blood. The microscopic appearance of the liver is illustrated in Figures VIII and IX.

Portal Cirrhosis.

Portal cirrhosis follows acute infectious hepatitis in 0·5% to 1·0% of cases (Neefe, 1954). It is characterized by excessive and irregular fibrosis of the liver, with disturbance of the normal lobular pattern. It may be inactive, in which case there are no biochemical abnormalities, or it may take an active form in which there is portal hypertension with or without hepatic failure.

After severe acute infectious hepatitis or acute yellow atrophy, complete recovery ensues if liver cell hyperplasia is able to restore the hepatic architecture before the reticulin framework of the liver is condensed and destroyed by fibrosis. Failing this, some degree of hepatic cirrhosis will follow. The acute stage of infectious hepatitis will thus rarely merge into a subacute stage of liver damage, in which necrosis and hyperplasia of liver cells are subordinate to fibrosis. Progressive fibrosis, however, can occur only with continuing parenchymal damage, and it is the rate of hepatocellular necrosis which ultimately determines the chronicity or acuity of the process.

In active cirrhosis the young fibrous tissue contains innumerable inflammatory cells, which are histologically indicative of progressive disease. In this active variety of portal cirrhosis, whether it be subacute or chronic (*i.e.*, rapidly or slowly progressive), there is always clinical and biochemical evidence of activity. The serum bilirubin level is raised in all cases, although the height of the serum bilirubin level is of no value in predicting a fatal outcome. The serum albumin level is always low—less than 3·4 grammes per 100 millilitres; a figure less than 3·0 grammes per 100 millilitres is of serious import.

The synthesis of hippuric acid is always impaired, but the degree of impairment bears no direct relationship to the degree of liver damage. The hippuric acid excretion test is therefore not a very valuable test. The response to the galactose tolerance test is impaired only in the more severe grades of active cirrhosis (Sherlock, 1946); but here the degree of impairment is in proportion to the extent of cell necrosis. In contrast to this, where the cirrhosis is not active—*i.e.*, where there is fibrosis of the liver, but with only a minimal cellular inflammatory reaction—the results of liver function tests are usually normal and regression is possible. The symptoms are similar to those of the post-hepatitis syndrome, and the differentiation can be made only by liver biopsy.

In the subacute form of hepatitis, the acute stage of the disease fails to subside, and death may occur after a delay of 10 or more weeks. Otherwise slow progression to active or inactive chronic hepatitis may take place, or alternatively recovery is possible. In fatal cases there is a gradual increase in the degree of hepatic insufficiency, which finally ends in hepatic coma with portal hypertension. The rate of clinical deterioration is proportional to the amount of inflammatory reaction in the liver. Sometimes the disease is so very slowly progressive that death may not occur until after a period of many years.

CASE III.—This case affords an illustration of a progressive, fatal subacute cirrhosis, which was thought to be a sequel to non-icteric infectious hepatitis. A male patient, aged 75 years, was first examined with the complaint of mild gastro-enteritis and diarrhœa. No note of jaundice was recorded at the time. He was given lead and opium pills, which he took for three months until he was examined again. He was now quite ill, with a hæmoglobin value of seven grammes per 100 millilitres, and examination of a smear of the peripheral blood showed marked stippling of the red cells. He was given three blood transfusions, and no jaundice was noted at any time after these. X-ray studies of the gastro-intestinal tract and sigmoidoscopic examination gave normal findings. Nine months after his first attack of diarrhœa he developed ascites, for which regular paracentesis was required. Occasionally he was found to have a temperature of 101° or 102° F. Nine months after first developing ascites he died. Examination of the liver showed the changes of subacute cirrhosis (Figures X and XI).

Primary Carcinoma.

Primary carcinoma of the liver is exceedingly rare, except as a sequel to or in association with cirrhosis. As far as Europe is concerned, it is agreed that primary carcinoma develops in 5% to 15% of patients suffering from cirrhosis (Symposium on Liver Disease, 1955). The incidence is, of course, much higher in other special racial and geographical groups, such as the Bantus and Orientals. If the incidence of portal cirrhosis following infectious hepatitis is accepted to be 0·5% to 1·0%, then from these figures the incidence of primary carcinoma following infectious hepatitis will be between 0·075% and 0·15% at at the most. (The average incidence of hepatoma in a series of autopsy cases has been reported at 0·2%, the material being unselected as regards previous liver disease—Lightman, 1942).

Figure XII illustrates the microscopic appearance of a nodule of primary carcinoma in the liver. It is distinguished from simple hyperplasia by the numerous mitotic figures and large pleomorphic nuclei. However, in some hepatomata with a good degree of differentiation, the distinction may be difficult.

The Carrier State.

The existence of a blood carrier state for homologous serum hepatitis is now well established (Neefe *et alii*, 1954; Stokes *et alii*, 1954). Even in those who eventually develop homologous serum hepatitis, there is a long asymptomatic incubation period during which the blood is infective. How this carrier state originally evolved is not known, because it is only since the introduction of modern parenteral therapeutic and diagnostic techniques that the virus has had the opportunity of circulating amongst the population. Whatever its mode of origin, this carrier state has produced a universal virus reservoir by means of which we unintentionally propagate the disease. The development of this carrier state may represent yet another facet of the changing pattern of disease (Engel, 1956).

Carriers of homologous serum hepatitis are invariably asymptomatic and in good health, and exhibit no abnormal biochemical changes in their blood. There is therefore no infallible screening test which will enable us to avoid their use as blood donors. However, the transmission of the disease can be diminished by the intelligent use of the various blood fractions which are now prepared by the blood transfusion service.

Whole blood must still be used for anæmia; but since it does not represent a pool from many donors, the danger of transmitting homologous serum hepatitis is limited to one recipient per donor. In the early days of pooled plasma one donor could contaminate hundreds of bottles of plasma and infect as many recipients (Table IV).

For shock unassociated with anæmia, serum albumin should be given, since in preparation this fraction will withstand the degree of heat required to destroy any virus which may be present. However, most of the virus is thought to be carried by the globulin fraction of plasma, and therefore the prophylactic use of gamma globulin for measles, poliomyelitis and infectious hepatitis theoretically involves some risk of transmitting homologous serum hepatitis. However, as now prepared by ethanol fractionation, gamma globulin appears to be virus-free.

Gamma globulin, while of value in the prophylaxis of infectious hepatitis, is useless in the prevention of homologous serum hepatitis, since there is no cross immunity between the two diseases.

Of the other blood fractions, the topical use of thrombin has been followed by serum jaundice.

Apart from the legitimate uses of blood and plasma, there are numerous other possible methods of transmitting homologous serum hepatitis. Any mechanism which involves the introduction of even minute amounts of blood or serum, dried or fresh, beneath the epidermis, involves risk. These mechanisms may include insect bites as well as the use of surgical instruments. Transmission by most of these other methods can be avoided with care.

Since the virus of homologous serum hepatitis is not found in the stools, fæcal carriers do not occur.

TABLE IV.

Showing the Risk of Contracting Homologous Serum Hepatitis when Whole Blood and Whole Non-Fractionated Plasma Pools are Used. (From Neefe, 1949.)

Material.	Incidence of Homologous Serum Hepatitus. (*Per Centum.*)
Whole blood	0·6 to 0·8
Small plasma pools (5 to 10 donors)	1·5
Large plasma pools (1000 to 5000 donors)	4·5 to 12·0

Carriers of the virus of acute infectious hepatitis are also known to exist, and in these individuals the agent is found in the stools as well as in the blood and may be transmitted by either vehicle. "Virus IH" may be present in the blood and fæces for a long period of time, perhaps for years, and often without symptoms (Neefe, 1954; Reimann, 1955). For this reason the absence of any history of contact is of no help in excluding the diagnosis of infectious hepatitis in a particular case. The carriers are frequently children ("Current Comment", 1955; Stokes *et alii*, 1954).

Hepatitis during Pregnancy.

It seems probable that the fœtus can acquire viral hepatitis by the transplacental route from the mother's blood, the infective agent usually being the "virus SH" (Sherlock, 1955). This is in all likelihood the natural mode of transmission for homologous serum hepatitis.

In cases in which the new-born infant has shown evidence of liver disease, the mother is often an asymptomatic carrier and can give no history of jaundice during pregnancy. New-born infants may also acquire infectious hepatitis during birth or in the neonatal period, and it is often difficult to decide whether one is dealing with a case of homologous serum hepatitis transmitted via the placenta during pregnancy or with a case of infectious hepatitis caught during the neonatal period. The difficulty is due to the wide difference in the incubation periods of the two diseases, and to the absence of a history of jaundice in the mother. What may appear to be a case of congenital homologous serum hepatitis developing a month or so after delivery may in reality be a case of infectious hepatitis acquired at birth.

There is some suspicion, but as yet no adequate evidence, that viral hepatitis, like rubella, may play some part in the production of congenital defects and stillbirths (Scott *et alii*, 1954).

CASE IV.—This case is an instance of premature delivery in a woman who developed infectious hepatitis during the sixth month of pregnancy. The infant weighed two pounds 14 ounces, and like the mother was deeply jaundiced at its birth. Its serum bilirubin content was 18 milligrammes per 100 millilitres. It lived only 18 hours, and sections from its liver were essentially normal, as would be expected if the disease was still in the incubation period.

This case therefore does not afford evidence of congenital infectious hepatitis, but merely of premature delivery due to hepatitis, with early death of the infant. This is a common complication of pregnancy (Sherlock, 1955).

Viral hepatitis may also simulate congenital biliary atresia, and in some cases the infants have been operated on for obstructive jaundice. A causal relationship is difficult to prove, but the virus may conceivably be responsible for the congenital defect of intrahepatic biliary atresia. The clarification of this point must await the development of a reliable serological means of diagnosing viral hepatitis.

Prevention of Sequelæ.

It has recently been denied that the incidence of serious liver disease is any greater after hepatitis than it is in persons with no such previous history ("Current Comment", 1955). Nevertheless, it has for long been a clinical impression that a diet of high caloric content and complete bed rest are essential during the acute stage of hepatitis if serious sequelæ are to be avoided. In the epidemics which followed World War II, it was firmly believed that a return to activity before complete biochemical and subjective recovery was attained would invite relapses, and that the insistence on bed rest would result in a milder course of the disease (Watson and Hoffbauer, 1947).

At least 95% of patients recover completely within four months; but because of the high morbidity of the disease, the numerical incidence of any sequelæ which occur may be higher than the percentages would lead one to believe. For this reason, most clinicians are still inclined to advise bed rest for long periods.

In 1947 doubts first began to be cast on the value of bed rest in shortening the course of the disease and in preventing the development of sequelæ, even when severe malnutrition was also present (Klatskin and Rappaport, 1947). Interest in this aspect of the disease was revived during the Korean campaign, when a large epidemic was investigated at a centre in Japan in an attempt to discover the optimum treatment with regard to bed rest and diet (Chalmers *et alii*, 1955). In this epidemic 0·2% of patients died during the acute stage of the disease and 0·7% developed chronic hepatitis. It was found that strictly enforced bed rest made no difference statistically to the outcome, but that patients treated with a diet rich in Calories (3000 to 4000) and protein (150 grammes), and supplemented by choline and vitamins, showed a more rapid fall in their serum bilirubin level and recovery was hastened. There was a tendency for the results of flocculation and turbidity tests to be more abnormal in the forced diet groups; but this was regarded as a feature of the diet rather than of the disease. Dietetic excess, however, is to be avoided in acute liver failure, in which much protein does harm rather than good.

These investigators suggest that the patient should be treated symptomatically as well as biochemically. They advised their patients to remain in bed as long as the acute symptoms persisted, and thereafter they were allowed up, regardless of the degree of jaundice, so long as they felt well. Strenuous activity was permitted as soon as the serum bilirubin level fell to 1·5 milligrammes or less per 100 millilitres and the retention of bromsulphalein was not more than 5% in forty-five minutes.

From these investigations it is concluded that a patient is best treated by rest during the acute stage, and thereafter by moderate activity according to his own subjective inclination. The diet should be adequate, but not excessive or forced.

The emphasis once placed on bed rest and a plentiful diet is merely an indication of the lack of any specific therapy. Gamma globulin is a prophylactic, but is useless in treatment. Sulphonamides may be harmful, and an effective antibiotic is still awaited. In acute yellow atrophy cortisone has been used with some success; but once its administration is started it must be used continuously until recovery is assured (Coleman *et alii*, 1954).

Caution must be employed before any revolutionary changes are made in the presently accepted methods of treatment of acute hepatitis, because the virulence of the agent in any particular epidemic cannot be assessed until the unfortunate sequelæ have made their appearance.

Summary

Infectious hepatitis is an ancient contagious virus disease which occurs in an epidemic and sporadic form and which is very difficult to control because of the lack of any specific means of diagnosis. With the elimination of typhus and enteric fever, it is now one of the last remaining scourges of military campaigns. It attacks the children and youth of all nations; but its numerical incidence varies greatly from country to country and from year to year. It is spread by fæcal contamination via the oral route, and close contact is usually necessary; but the incidence diminishes as active immunity is acquired later in life.

It is more prevalent in the autumn and early winter in temperate climates, but the reason for this is not known.

Sequelæ rarely follow infectious hepatitis, but when they do they may be serious. The complications include anxiety neurosis, fulminating massive hepatic necrosis and portal cirrhosis, either latent or active. The histological features of these complications are illustrated.

Homologous serum hepatitis is a similar but more severe disease caused by a different virus. It can be transmitted only by the direct introduction of infective blood beneath the epidermis. Its epidemiology is quite different from that of infectious hepatitis, but its sequelæ are the same.

Probably nothing which we can do at present will influence the incidence of sequelæ in infectious hepatitis, and there seems to be no need meanwhile for any radical changes in current treatment. The whims of the patient should be considered in the matter of diet and early ambulation.

Acknowledgements.

Table IV is reproduced from Neefe (1949), by permission of the author and of the editor of *Annals of Internal Medicine*. Figure I is taken from Paul and Gardner (1950), and is reproduced here by permission of the authors, and of the editor of *The American Journal of Medicine*.

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Legends to Illustrations.

FIGURE V.—Acute infectious hepatitis: portion of a liver lobule. The upper half of the figure shows viable liver cells at the periphery of the lobule. Many of these cells have large, prominent nuclei indicating hyperplasia, but mitoses are absent. A few cells have cytoplasmic vacuoles representing fatty change; dark green bile thrombi are present within canaliculi. The lower half of the figure represents the centre of the lobule. Here the liver cells have disappeared and have been replaced by œdematous connective tissue containing phagocytes laden with bile pigment.

FIGURE VI.—Persistent portal scarring following acute infectious hepatitis. The portal tracts are greatly expanded and fibrosed, and contain a marked excess of lymphocytes. There is no great proliferation of bile ducts, and the portal tracts are expanded by lymphocytic infiltration rather than by excessive fibrosis. It is therefore unlike true cirrhosis.

FIGURE VII.—Liver in subacute infectious hepatitis. There is extensive necrosis of the liver, which affects particularly the central portions of the lobules. The only remaining liver parenchyma is a narrow zone of cells surrounding the portal tracts. This has produced the appearance of false lobules, in which the portal tracts are situated at the centres of the lobules instead of the hepatic veins. The reticulin framework is preserved, and complete recovery is theoretically possible.

FIGURE VIII.—Liver in acute yellow atrophy (low power of the microscope). There are some islands of liver tissue still surviving, but most of the liver parenchyma has been replaced by hæmorrhagic granulation tissue. The necrosis displays no tendency to a zonal distribution, but is diffuse and widespread.

FIGURE IX.—Liver in acute yellow atrophy (high power of the microscope). On the lower half of the illustration, the liver cells have undergone necrosis and absorption and have been replaced by a hæmorrhagic granulation tissue. On the upper half of the illustration there is regeneration of liver parenchyma from surviving cells, but this is imperfect, and the new epithelium resembles that of bile ducts.

FIGURE X.—Liver in subacute cirrhosis (low power of the microscope). Complete disorganization of the liver; irregular islands of liver parenchyma surrounded by connective tissue abundantly infiltrated by lymphocytes.

FIGURE XI.—Liver in subacute cirrhosis (high power of the microscope). Individual liver columns surrounded by connective tissue containing numerous lymphocytes and a few engorged capillaries. The portal tract shows an increase of cells and connective tissue—*i.e.*, active cirrhosis.

FIGURE XII.—Liver: primary carcinoma. The malignant cells have large pleomorphic nuclei, and several mitotic figures are present. One atypical "T"-shaped mitosis can be found on the left edge of the figure close to the upper left-hand corner. In the extreme lower part of the figure, the carcinoma is bounded by a band of connective tissue containing a few groups of non-malignant liver cells and a few lymphocytes.

INFECTIOUS HEPATITIS: REPORT OF AN OUTBREAK, APPARENTLY WATER-BORNE.

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WHEN several cases of infectious hepatitis occur in close relationship to each other, as in members of a family or inmates of an institution, it is the practice of this office to carry out an investigation.

The following cases are of interest, especially with regard to the likely source of infection. The circumstances briefly are these.

On Friday, May 3, 1957 (Show Holiday in Bathurst), a party of 20 students (aged 17 to 19 years) from one of the colleges in Bathurst went on a picnic hike to Mount Pleasant, which is situated about four miles north-west of the town. The weather was warm, and the students, playing sports, became thirsty. Nineteen drank raw water from the nearby Macquarie River in amounts varying between a few mouthfuls to a few cupfuls taken at various times between 11 a.m. and 4 p.m. This river is polluted by the Bathurst sewage treatment works situated a half-mile north of the town. The works, which serve approximately 14,000 people, are grossly overloaded; the effluent is of unsatisfactory quality with much suspended humus. The effluent, before its entry into the river, is chlorinated, but insufficiently, as shown by check tests for residual chlorine and the presence of fæcal organisms.

Fifteen of the students who drank the water developed gastro-intestinal upsets two to five days later, with vomiting, some diarrhœa and loss of appetite. The symptoms generally were not severe, and only one of the students consulted a doctor, who told her she had "a germ in the bowel". No laboratory tests were carried out.

Approximately four to five weeks after the picnic, and within a few days of each other, five of these students developed infectious hepatitis, presenting the usual symptoms including jaundice. The amount of water that had been consumed by these varied One stated that she had had only a few mouthfuls. The cases were notified by the attendant medical practitioner to the local health authority (Bathurst City Council). Five other students of the party had transient suggestive symptoms (nausea, loss of appetite, feeling out of sorts, undue tiredness), but developed nothing further, except one whose symptoms progressed. Subsequently her own doctor in Sydney notified her as suffering from infectious hepatitis. This made a total of six notified cases.

The college authorities were concerned that the infection might spread widely. There are about 300 students resident in the college and some staff. The college up till then had had a history fairly clear of infectious hepatitis (three cases in several years, the last case occurring in a staff worker who had left the college some months previously). However, it soon became clear that the students who had reported sick and were diagnosed as suffering from infectious hepatitis were only those who had gone on the picnic.

It was considered that all the remaining students who had drunk the water were potential sufferers from infectious hepatitis. They were interviewed individually by the writer for epidemiological information and were given gamma globulin prophylaxis by their medical attendant (Dr. Eric Greenacre) on June 12, 1957. The use of gamma globulin was extended to the following: the room mates of all the students who had gone on the picnic (there are three and sometimes four students to each room), the cleaning staff of the dormitories concerned, and others who had close contact with the affected students before the condition was diagnosed—namely the matron of the college hospital, her assistant, and student friends of the patients, who had done their washing for them. About 50 people in all received gamma globulin, two cubic centimetres each. No secondary cases developed among the college contacts.

None of the six patients had ever had infectious hepatitis before, and none gave any history of blood transfusion or significant injections. Full inquiry ruled out any likely source of infection other than the river water. In this connexion, 10 cases of infectious hepatitis were notified in Bathurst for the four months preceding May for the year 1957, and most of these patients would have been served by the sewer. Three had been admitted to hospital, one on May 2, the day before the picnic. The season was a dry one and the river was very low, with relatively much less dilution of the sewage than would ordinarily exist. Tests were made of the sewage effluent after this outbreak, with the following result.

Bacteriological examination showed gross contamination with fæcal coli, in spite of the fact that chlorine, at the rate of 42 pounds by weight per day, was being fed into the effluent as it left the works, and tests with both "Chlorotex" and orthotoludine showed no residual chlorine in the effluent. The opinion formed was that the effluent was of such unsatisfactory quality as to "mop up" all the available chlorine.

The local authority was advised of these findings and asked to erect notices along the course of the river at strategic points warning picnickers of its unsuitability for drinking and swimming, to enlarge the existing works as soon as possible, and to increase the chlorine dosage to give a residual figure of one to two parts per million in the effluent.

Discussion.

This outbreak, and the unsatisfactory sanitation found, prompted the writer to review the available literature on apparently water-borne epidemics of infectious hepatitis. Several such outbreaks have been studied and recorded, the most comprehensive and conclusive investigations being those of Neefe and Stokes (1945). These workers studied an epidemic of infectious hepatitis which occurred during the late summer of 1944 in a large camp for boys and girls near Philadelphia. Three hundred and fifty of 542 persons developed hepatitis within a period of 13 weeks. Infection was traced to drinking water obtained from a well contaminated by a cesspool. By feeding volunteers with this water, a mild illness associated with hepatic dysfunction was produced.

Among other water-borne outbreaks, some of which were very carefully studied, though without the demonstration of infectivity on volunteers, are those reported by Fraser (1931), in which the source was a fæcal-polluted spring; Harrison (1947)—a fæcally polluted well; Farquhar and others (1952)—a well contaminated by a cesspool; Tucker and others (1954)—a sewage-polluted spring; Archer (1954)—pollution of a pure supply by cross-pipe connexion with a sewage-polluted river supply; Peczenik and others (1956)—pure hotel drinking water polluted by cross-pipe connexion with a subsidiary supply, cesspool contaminated. Wilson (1957) reviewed 72 cases in an outbreak occurring between April, 1955, and August, 1956, at Renmark on the River Murray in South Australia. He noted that spread of the disease tended to occur along the major irrigation channels, water from which might be used for drinking, and suggested pollution of the water by pan sewage as a cause.

In most of the above-quoted outbreaks, considerable numbers were affected, and the cases occurred almost simultaneously and ceased to occur when the suspected water supply was no longer used. In some the infectious hepatitis outbreak was preceded by gastro-intestinal disturbance, as in the present series. Harrison comments on the close parallelism between the incidence curves of diarrhœal disease and infectious hepatitis cases seen in the Mediterranean area during the second World War. Neefe and Stokes, commenting on the epidemic they studied, were struck by "the apparent ease with which the infectious agent was acquired at the camp in contrast to the apparent lack of ease with which it was acquired by those in contact with infected persons away from the camp". The Bathurst outbreak here reported was confined to primary cases apparently infected from a common source. Fortunately, no secondary cases occurred in the college, even though dormitory rooms were shared with numerous other students in the early stages of the disease. Peczenik, besides clinical screening of persons exposed, also carried out a careful laboratory screening, in this way uncovering additional cases. No such laboratory screening was done in the present series, though this would have been of interest and value. In some of the recorded outbreaks the water had been chlorinated. This measure, according to studies conducted by Neefe and others (1945), would not have been a protection. By treating water known to be infective and feeding it to volunteers, Neefe found that the customary amount of chlorine used in the chlorination of water supplies does not inactivate or attenuate the virus of infectious hepatitis. On this basis, one would not expect that chlorination of sewage effluent would render it free of infectious hepatitis virus.

Comment.

The outbreak here reported emphasizes the danger of drinking raw water from streams of doubtful purity, and the need for hygienic disposal of human excreta. Where several cases of infectious hepatitis occur together, it is worth while having a full inquiry made for a possible common source of infection. To effect this, the disease should be promptly notified to the local health authority.

Summary.

An outbreak is reported of gastro-enteritis followed by infectious hepatitis, affecting students in a residential college, the infection in both cases apparently coming from a common source—the drinking of raw water from a river polluted by sewage. Of 19 people (aged 17 to 19 years) who drank raw river water, 15 developed gastro-intestinal upsets two to several days later, and six developed infectious hepatitis 26 to 38 days later. Of those who did not develop infectious hepatitis, 13 in number, five had symptoms of significant constitutional upset (undue tiredness, headache, nausea, anorexia) 37 to 43 days later. All these 13, and one who was subsequently diagnosed as suffering from infectious hepatitis, were given gamma globulin 40 days after drinking the river water. The use of gamma globulin was extended to room contacts of those who drank the water. No secondary cases developed in the college. Outbreaks of apparently water-borne infectious hepatitis recorded in the literature are discussed.

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Addendum.

As this article goes to press, a report has just come to hand of a governmental inquiry into a widespread outbreak of infectious hepatitis affecting many thousands of people in Delhi, India, in December, 1955, and January, 1956. Evidence showed this outbreak to be caused by the city water supply's becoming contaminated with sewage near the point of its intake from the Jamuna river, the virus surviving the filtration and chlorination processes to which the water was subjected as a routine. (Government of India, Ministry of Health publication, 1956—Report of Committee of Inquiry.)

THE EVALUATION OF TREATMENT.[1]

By R. R. H. LOVELL,
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IT goes without saying that when a doctor advises or gives treatment, he believes that he is doing something which benefits the patient. He believes that, by virtue of his treatment, the patient's disease will be more rapidly or more completely relieved than it would have been if the treatment had not been given. The key phrase here is "the doctor believes", and it is the basis of this belief that I am going to consider.

Some aspects of this topic have been discussed in recent years, notably by Hill (1950-1951), Gaddum (1954), Green (1954) and Reid (1954). I shall draw freely from their wisdom. But most of those who have discussed the topic have not been clinicians, and it is primarily from the clinician's viewpoint that I shall speak.

Belief in the value of a treatment is usually based chiefly on one of three things: the opinion of authority, the light of experience or the result of experiment. I say "chiefly", because this is an over-simplification. Authority and experience in particular are usually intermingled, and it has been truly said that the treatment of every patient is virtually an experiement (Brunton, 1887; Pickering, 1949). However, the over-simplification is a convenient one, and I am first going to consider in turn the ways in which these factors, authority, experience and experiment, influence the reputation of methods of treatment.

Authority.

Authority has influenced the reputation of many treatments over many years—since, in fact, the role of healer was first assumed by the ancient tribal priests. As an early example of the operation of authority, I will tell you the story of Dr. John Geynes. Galen is often regarded as the "Father of Therapeutics". He died in A.D. 201. His authority was still paramount some thirteen centuries after his death. In 1559, John Geynes, an Oxford doctor of physic, questioned Galen's authority. For his temerity, he was required to bring to the notice of the College of Physicians in London all the passages of Galen's works which were erroneous (Greenwood, 1936). This had to be done within one month. There were apparently some 82 surviving works and all of them were bulky. Though it is regrettable, it is

[1] From an inaugural lecture of the James Stewart Professor of Medicine, delivered at the University of Melbourne on May 6, 1957; also delivered to the New Zealand Branch of the British Medical Association at Christchurch, New Zealand, on August 8, 1957.

perhaps not surprising that Dr. Geynes declined the task and, as *Greenwood* has said, "subscribed a handsome apology to the dead dictator". This is an example of authority maintained by tradition. Happily it is hard to conceive of our Royal Colleges behaving in this way today. But authority still operates.

In our own time the use of gold in tuberculosis has provided an example. This was a treatment whose evaluation was obscured by the authority of unsound theoretical considerations. Gold was said to slow the growth of tubercle bacilli and to modify the inflammation which they cause. It became popular in 1924, and it remained fashionable for about 15 years. This is indicated in Figure I, which was prepared by Hart (1946). It shows

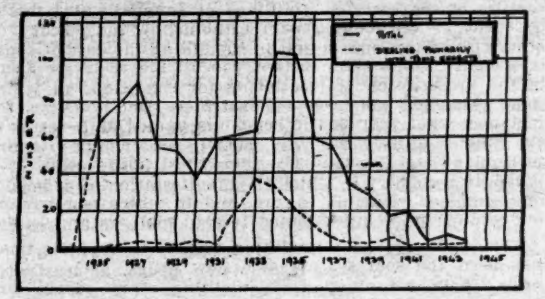

FIGURE I.

Graph showing the number of papers on gold treatment in tuberculosis listed in the *Quarterly Cumulative Index Medicus* during the years 1925 to 1944 (after Hart, 1946).

the annual number of papers listed in the *Quarterly Cumulative Index Medicus* from 1925 to 1944 on the treatment of tuberculosis with gold. In spite of all the papers written about it, the value of gold was never established over these 20 years. Furthermore, gold is poisonous. The toxic effects are all serious, and before the days of British anti-lewisite, some were fatal. An appreciation of the toxicity of gold is also reflected in Figure I. When we come to consider the ethics of modern methods of testing treatments, it is well to remember the harm which may be caused by a treatment of no proven value, the only sanction for whose use is authority.

Since the influence of authority is wholly bad, it is useful to recognize its contemporary sources. These include the following.

1. Medical authorities. These are such people as Hippocrates, more recently dead and respected doctors, late members of our own hospital staffs and, as important as any, contemporary medical teachers. Contemporary teachers unhappily sometimes appear to students as infallible oracles. My friend and teacher, Professor Pickering, is fond of quoting the Dean of Harvard as saying: "I tell my students: in ten years' time half of what you are taught will have been shown to be wrong, and the trouble is that neither I nor any of your teachers knows which half."

2. Text-books. Text-books, like teachers, can be unassailable sources of authority. They can conserve therapeutic shibboleths from edition to edition and so from generation to generation.

3. Brochures supplied by drug manufacturers. These could provide useful evaluations of treatment, though for obvious reasons they often do not. The influence of brochures advertising drugs may be considerable, in particular among busy practitioners. Brochures present information in a concise and often æsthetically attractive form, and they appear to spare a busy man the need to examine critically such claims as are made.

4. The Press. By the Press I mean that section of the lay Press which sometimes prints unwarrantably enthusiastic evaluations of treatments. In some countries, the evaluation of treatment in this medium can lead to such pressure on practitioners that they find it hard to resist the dictates of their patients. Happily this does not appear to be the case in Victoria.

5. Authority derived from well-known recipients of a treatment. This may obscure its proper evaluation for many years. The waters of spas in the treatment of rheumatism, and mountain air for the treatment of tuberculosis are medical examples of such derived authority. It might be called the authority of fashion. The crop of appendices which was harvested for years after Sir Frederick Treves's operation on King Edward VII was reputed to be enormous; a fashion in surgery was established which was, I think, still evident up to the time of the last war.

These then, are some of the contemporary sources of authority. It is a bad basis for evaluating treatment. Perhaps it was the depressing outlook that it engenders which provoked Oliver Wendell Holmes to tell his medical students: "I firmly believe that if the whole *materia medica* could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes."

Experience.

Experience is the second common basis for the evaluation of treatment, and of course it forms the basis for much authority. By experience I mean the repeated observation of the course of a disease treated in a given manner. Evidence derived from experience is usually of one of two sorts.

The first sort is based on the proposition that patients with such-and-such a disease who are treated with rest, or exercises, or radiant heat, or deep X rays, or diet, or a drug, appear to do well; therefore that treatment is effective. Now, this sort of argument often takes no account of the course of the disease in comparable patients who do not receive the treatment. Consider the following figures which show the results obtained when 173 patients were given the same new treatment for the common cold.

Number of patients treated	173
Percentage cured	14
Percentage cured or improved	65
Percentage of unpleasant effects attributed to treatment	19

Tablets were started on the first day of symptoms, and the patients' and doctors' opinions were recorded daily. On the second day 65% of the patients were either cured or improved. This might seem to be striking evidence of the value of the tablets. Certainly 19% had unpleasant symptoms, which they attributed to the tablets. This high incidence of what appear to be side-effects is not, however, the reason why the drug is never marketed as a cure for colds. In fact, these results were obtained with dummy tablets which contained no active substance at all. (Medical Research Council Committee, 1950.)

The second difficulty in using experience as a sole yardstick is that it often takes no account of the influence on the disease of factors other than the treatment itself; of the emotional effects of the doctor's visits, of enforced solitude, rest or exercise; or of the attractive young ladies who give physiotherapy. All these may be relevant factors.

Surgical treatment is specially susceptible to uncritical evaluation by experience. After a major surgical operation, neither the patient nor the surgeon may be in a particularly good position from which to take an entirely unbiased view of the results, and this may be especially true, at least so far as the patient is concerned, if a fee has been involved. It is salutary to reflect on the numbers of patients who have been submitted, for instance, to removal of tonsils or even to such a major procedure as sympathectomy for high blood pressure under circumstances in which the value of the operations has remained in doubt.

The treatment of peptic ulcer provides a medical example of the difficulty of evaluating treatment in the light of experience alone. Many measures are used in treating peptic ulcers, some of which are as follows: (i) physical rest; (ii) the allaying of anxiety; (iii) frequent meals of "bland" foods; (iv) intragastric drip administration of milk; (v) administration of barbiturates; (vi) the use of

alkaline medicines and lozenges; (vii) the exhibition of drugs supposed to reduce gastric secretion; (viii) the exhibition of drugs supposed to reduce gastric motility; (ix) the administration of vitamins. It is a common impression, derived from experience, that the symptoms of peptic ulcer are relieved, and that healing is promoted, by some or by all of these measures. Some doctors use some of them, some all of them.

Now, multiplicity of treatments should always make one suspicious of their value. In fact, some of these treatments have lately been critically reappraised. The question of diet may be taken as an example. Lawrence (1952) has studied what he considered to be two comparable groups of patients with peptic ulcer. All were treated similarly, except that one group received the Lenhartz type of "ulcer diet" and one a full normal diet. Radiological healing of the ulcer was claimed in 93% of cases in both groups. The mean time of radiological healing was a little shorter in the group taking a normal diet than in the group treated with the special diet, though this difference is probably not significant. The mean time for abolition of pain was virtually the same in both groups. So this experiment provided no support for the idea that the special diet benefited Lawrence's particular patients under the conditions of his study. If other studies with more patients under other conditions produce similar results, we shall have to agree that our evaluation of the place of diet in the treatment of peptic ulcer has been erroneous. If, in fact, our estimate of the importance of diet is shown to be erroneous, we shall have achieved something. Dietary restrictions on our patients may be eased. But, even more important, new thoughts will be provoked in our own minds on the nature of the factors which really do promote the healing of ulcers.

This example of the difficulty of evaluating treatment by experience alone could be multiplied many times in every branch of medicine. But some evidence which is derived from experience, may be more compelling. This is the case when the effects of a new treatment are conspicuously different from effects seen before. For example, the immediate value of penicillin in lobar pneumonia and that of cortisone in certain inflammatory diseases of the eyes were apparent to those who first gave the drugs. This sort of evidence is really like that obtained in a therapeutic trial using retrospective controls, which I shall discuss shortly, for the effects of the treatment are compared with the course of disease seen previously.

Clearly experience can, and often very rightly does, play a decisive part in evaluating treatment; and there are examples of some serious diseases in which experience with a new treatment establishes its value so quickly that a trial in which the treatment is withheld from a similar group of patients for purposes of comparison is quite unjustifiable. But the limitations of experience as a means of evaluating the effects of treatment must be remembered, and these limitations are particularly important when a chronic disease with a variable natural course is the object of the study. I shall make further comments about this later.

Experiment.

Some otherwise thoughtful people react with considerable emotion when one introduces the word "experiment" into the context of medical treatment. It evokes in them a feeling that there is something vaguely improper or morally wrong in experimenting in this sort of field. This outlook, carried to its logical conclusion, would mean that it is more respectable to die while receiving an apparently established treatment than to risk recovery trying out a new one. But it must be clear to you that the evaluation of treatment by authority and experience, though these appear respectable enough yardsticks, not only is extremely imperfect, but can be positively dangerous.

I am going to describe to you the meaning and nature of the experimental method as applied to the evaluation of treatment, and then say something of the ethical and practical implications. But by way of introduction I would remind you that until quite lately therapeutics has masqueraded as an art, and it is worth while briefly to consider some of the factors which have caused it to be unmasked, and which have led to its being recognized for what it is—that is, an experimental science.

I suppose the fundamental factor has been the increasingly critical attitude of medical teachers towards the value of many accepted methods of treatment. This critical attitude, in turn, has been stimulated by many factors. The growth of the pharmaceutical industry in the last few decades has been enormous. Thousands—probably hundreds of thousands—of new biologically active substances are being produced every year. Many of these, on theoretical grounds, merit critical appraisal in human disease.

Another factor has been the economic one. Many modern and effective methods of treatment are extremely expensive. No one would wish to deprive any patient of their benefit because of the cost. But millions of pounds, which might be spent by a community in establishing the efficacy or otherwise of treatments and in sustaining the cost of those treatments which are effective, can all too easily be spent in the prescription of treatments for conditions in which their value has not been demonstrated. One wonders, for instance, what therapeutic benefit is gained as a result of the roughly £2,000,000 a year spent in prescribing vitamins in England and Scotland (Dunlop *et alii*, 1953)—this, be it noted, in a country in which the manifestation of deficiency of recognized vitamins is rare, and in which cod-liver oil and orange juice are supplied free to mothers and babies.

Yet another factor stimulating critical therapeutic trials has been the scarcity of some new drugs, at least soon after their introduction. Penicillin, streptomycin and cortisone are familiar examples in which scarcity has prompted early critical studies.

A further factor has been the development of statistical methods by which biological data may be handled more economically in terms of time and material than has previously been the case.

And I would certainly add as a potent factor a higher level of education among patients, who are nowadays by no means entirely contented by the prescription of an elegantly flavoured concoction.

The meaning of experiment in the context of trials of treatment differs in no way from its meaning in other branches of science. The essence of an experiment is that observations are made under a fixed set of conditions, and the effect of altering one condition at a time is then observed. To become meaningful, the effects must occur more frequently than might be attributable to the play of chance alone.

The Therapeutic Trial.

Translating this to therapeutics, the object of a therapeutic trial is to discover whether patients who receive a treatment ar benefited more frequently, more completely and more rapidly than they would have been without the treatment. The essence of the trial is that a comparison is made between a group receiving a particular treatment and a group not receiving it. The group not receiving it is called the control group. Both groups of course receive the same basic treatment, which is the best recognized for their disease.

A therapeutic trial of this sort is not a new invention. James Lind carried out a controlled trial of treatment in scurvy 200 years ago. It was so beautifully done that some of his own words are worth quoting (Lind, 1753):

> On the 20th May, 1747, I took twelve patients in the scurvy on board the "Salisbury" at sea. Their cases were as similar as I could have them . . . They lay together in one place being a proper apartment for the sick in the fore-hold and had one diet common to all . . . Two of these were ordered each a quart of cyder a day . . . Two others took twenty-five drops of elixir of vitriol three times a day . . . Two others took two teaspoonfuls of vinegar three times a day . . . Two of the worst patients were put upon a course of sea-water. Of this they drank half a pint every day . . . Two others had each two oranges and one lemon given them every day . . . The two remaining patients took . . . an electuary recommended by a hospital surgeon made of garlic, mustard, balsam of peru and myrrh. The consequence was that the most sudden and visible good effects were

> perceived from the use of oranges and lemons: one of those who had taken them being at the end of six days fit for duty . . . The other was the best recovered of any of his condition; and being now deemed pretty well was appointed nurse to the rest of the sick.

This is not the occasion for a detailed description of the many factors which have to be considered in designing a controlled trial of a treatment. But I will mention some of the factors briefly.

In planning such a trial, it is necessary to decide the right things to measure. Sometimes they are fairly fundamental, like recovery or death. Often they are such things as fever, body weight or muscle power.

Then the appropriate method of controlling the trial has to be decided. In some chronic diseases, it is possible to use the patient as his own control. After a period of observation, the treatment being tested is given. It is then stopped, and the patient's condition during the period of treatment is compared with his condition during periods without it. There are several variations on this theme.

There are objections to this method of individual control. Many chronic diseases fluctuate in their severity, and it may be hard to distinguish natural remissions from treatment effects. It is also hard to keep incidental emotional and environmental factors constant. Unless, therefore, treatment effects are rapid and dramatic, trials based on individual controls may be unconvincing.

Retrospective controls are sometimes used. This involves comparing the course of a disease treated in a given way with its course in patients previously studied without the treatment. Such trials are rarely conclusive, because it is hard to match patients in the two groups for all factors other than the treatment being tested. They may, for instance, differ in sex, age or social status. The other difficulty is that the natural history of the disease may have altered. For instance, diphtheria has killed fewer people since the introduction of active immunization. But during this time scarlet fever has become less fatal. There is, in fact, good evidence to support the idea that immunization against diphtheria does reduce its mortality, and we do not know why scarlet fever is less fatal than it was. But on the retrospective evidence alone, it would clearly have been unwise to attribute the reduction of deaths from diphtheria to immunization (Gaddum, 1954).

A trial using simultaneous controls gets over many of these difficulties and is probably the most efficient means of evaluating treatment. It involves the random allocation of patients to a group receiving the treatment under investigation and to a group not receiving it. Alternatively, patients in the treated and control groups may be selected by matching them for age, sex and severity of disease. All treatments other than that being tested must be identical in the two groups.

A very real difficulty may arise in this sort of experiment if patients and their attendants know which is the group receiving the remedy under test and which is the group not receiving it. Experience has shown how great the effects of many so-called treatments are when they are new. Hence the aphorism ascribed to Trousseau, a nineteenth century French physician: "Let's hurry, hurry, use the new drug before it stops curing."

To overcome this difficulty, a so-called double blind test may be appropriate. Patients are asked to cooperate in the trial of a remedy, on the understanding that they may or may not themselves receive it. The treated group receives the drug, say a tablet, and the control group receives an indistinguishable dummy tablet, which is pharmacologically inactive. The doctors and nurses treating the patients are unaware, until the trial is over, which individuals are receiving the new drug and which are receiving the dummies.

Considerable ingenuity may have to be exercised in carrying out a trial of this sort. The perfect trial is sometimes quite hard to achieve, and it can be a little disappointing to hear, as I did once, a patient calling across the ward to his friend: "Which treatment are you having, the real stuff or the dummies?"

In carrying out this or any other sort of planned trial of treatment, the results should be submitted to the same standards of testing as are applied to other biological data. The first yardstick is that of common sense. The second is the use of statistical methods to test whether any effects measured in the patients treated with the remedy under test occur more frequently than can be accounted for by chance, as illustrated in the control group.

Most clinicians are inadequately trained in statistical methods applicable to biology. Most of us are forced to know a good deal more about the statistics of accountancy. A statistician is therefore an important partner at all stages of the trial. Before a trial is started, he can often help with a forecast of the number of patients likely to be involved before a clear answer about the value of treatment may be expected. The statistician's knowledge is invaluable in the early stages of planning, as it is in helping to handle the results at the conclusion of the trial.

Limitations of Controlled Trials.

Controlled therapeutic trials have sometimes been accepted with unwarranted enthusiasm, sometimes with a good deal of criticism. I want, therefore, to say something of their limitations.

The first limitation is that they give information about the average reaction of a group of patients, while what the clinician really wants to know is the specific reaction of his individual patient. This is, of course, no argument against controlled trials. Indeed, it is the very fact that patients do respond variably which makes such trials necessary. I would emphasize, however, that knowledge of the average response of patients can most usefully be applied in the light of experience gained in individual patients. There is no substitute for such experience. A knowledge of the statistical evaluation of treatment is not the be-all and end-all of successful therapeutics.

The second limitation is that, after a great deal of work, an answer may be obtained to only a limited question about a restricted group of patients. Controlled therapeutic trials have come in for a good deal of criticism because this limitation is not properly appreciated. I suppose this has never been more apparent than in the evaluation of cortisone in chronic rheumatic diseases. For instance, certain manifestations of certain stages of rheumatoid arthritis appear to be no better controlled by certain doses of cortisone than they are by certain doses of aspirin (Joint Committee of the Medical Research Council and the Nuffield Foundation, 1954). This is clearly established. But it must be remembered that the trials do not pretend to indicate what would be the effect if the same or another dose of cortisone had been given in a different stage of the disease. This may seem to be so obvious as scarcely to deserve mention; but it is on this very point that misapprehension is surprisingly widespread. By their nature, controlled trials can usually answer only very limited questions, and in assessing their results, the questions asked must be constantly remembered.

A third limitation is that trials, as at present carried out, often involve a large number of patients before a clear-cut answer is provided. The limiting factor here lies in the realm of the statistical technique employed. It is important that we clinicians should not be complacent about the statistical methods at present available. We should ever be spurring on our statistically minded colleagues to streamline existing methods and to evolve new ones.

Ethics of Therapeutic Trials.

I come next to some ethical considerations, which are inseparable from a discussion of the evaluation of treatment. It is important that we should think clearly about this matter.

My thesis has been that the evaluation of treatment is properly a scientific procedure. Now clinical science differs from other sciences in one very important respect. In clinical science, the appropriate and often crucial experiment may be one which is morally wrong if it is applied to the subject we study, which is man. Anyone who has done any clinical research will have been forced to ponder this question at one time or another.

Ethical questions always arise when the testing of treatment is discussed. I agree with Green (1954) that in mild illnesses, like the common cold, no difficulties arise provided, first, that volunteers are used, secondly that they are told that they may or may not receive the drug being tested, and thirdly that the investigator is satisfied that the test and control materials are safe.

The position is much more difficult to define when a remedy is being tested which may make a difference between life and death or between a long illness and quick recovery. Under these sorts of circumstances, I think it is often desirable that several doctors should discuss the nature of the study, for it is possible that the enthusiasm of an individual may mar his judgement. The background of the discussion should be that, "where the value of a treatment, new or old, is doubtful, there is often a higher moral obligation to test it critically than to prescribe it year in, year out, with the support merely of custom or of wishful thinking" (Green, 1954).

If a trial of treatment is to be carried out, it must be designed so as to be as efficient as possible. In particular, it should be efficient in using as small a number of patients as is possible. The final yardstick must always be that the doctor will never give his patient any treatment which he would not willingly take himself or give to his children under similar circumstances.

The Future.

I have spoken of the past and the present. This is a field in which the application of the methods of experimental science can be very rewarding, as was shown by James Lind two hundred years ago and has been more amply demonstrated in the last ten years.

In the method of the controlled trial of treatment, we have a means for testing different remedies. But it will be clear, from what I have said, that controlled trials take up much time — time in discussion, time in planning, in organizing, in execution, and in interpretation. Because they are time-consuming, they are also expensive. In addition, therapeutic trials often involve team-work and forbearance of a high order among doctors. An efficient trial demands a steady flow of patients for study. This can often be ensured only if doctors agree among themselves to forgo for a while the treatment of the disease in question so that a colleague studying it may handle enough cases. Trials always involve enthusiasm and effort sustained over months, and in the case of chronic diseases over years.

In my view, the many difficulties in conducting trials of treatment in acute and chronic diseases can be overcome. The clinical departments of the universities should be places where a lead may be given in trying to surmount the difficulties. I regard the promotion of the critical evaluation of treatment as one of the proper functions of these departments today.

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RECURRENT PYURIA IN CHILDREN.[1]

By L. D. WHEELER,
Sydney.

THE function of the urologist in the investigation and treatment of recurrent pyuria in children is to demonstrate if possible underlying abnormality in the urinary tract, including the common congenital anomalies; he must have as his guiding principles, first, that the renal parenchyma must be conserved and guarded against any further damage, and secondly, that the patient's symptoms must be relieved and the patient's urine must be rendered cell-free and sterile.

Megaureter.

Megaureter, although not one of the common causes of pyuria, is probably the most serious. In the past, megaureter has been regarded as essentially due to bladder-neck or posterior urethral obstruction, and attempts have been directed towards correcting bladder-neck stenosis, posterior urethral valves, etc. However, the work of Douglas Stephens at the Royal Children's Hospital, Melbourne, and overseas has brought a new approach to this problem, and whatever the basic lesion, his concept of reflux up the ureter (the megaureter can here be regarded as a bladder diverticulum) is of great use in investigation and treatment. Stephens (Stephens, 1954) described his technique of micturition cystourethrography to demonstrate reflux in megaureter, and from his studies of the emptying time of these ureters he advocated "triple micturition", in which the child is encouraged to micturate in three successive acts at the one sitting with two-minute intervals between. In this way Stephens found that he could empty the megaureter and control the associated urinary tract infection.

Duplication in the Urinary Tract.

Duplication in the urinary tract is associated with an increased incidence of urinary tract infection; but for a moment we may consider the current terminology associated with urinary tract duplication. Higgins, Williams and Nash, of Great Ormond Street (Higgins, Williams and Nash, 1951) use the word "pyelon" ("a receiving vessel") to signify a unit of ureter, renal pelvis, calyces and collecting tubules. *Pyelon simplex* describes the normal condition of the upper part of the tract, while *pyelon duplex* covers the forms of duplication. *Pyelon duplex* may be complete or incomplete (bifid ureter). These same authors speak of the larger (that is, lower) renal component with the ureter opening in the normal (orthotopic) position as the "proto-pyelon", and the secondary pyelon with the ureteric orifice in the ectopic position as the "deutero-pyelon". Here it is interesting to recall the normal (although not invariable) arrangement seen in complete *pyelon duplex* — namely, that the lower and larger renal component of renal tissue drains by a ureter which opens at a position medial and caudal to the normal orifice, as recognized in the "Weigart-Meyer law" quoted by Macalpine (Macalpine, 1949). Duplication takes one of the following four forms: (i) orifice of the deutero-pyelon outside the urinary tract (classical "ectopic ureter"); (ii) ectopic orifice opening in the urethra, female or male (in the latter instance the ureter will open into the ejaculatory duct or seminal vesicles); (iii) ectopic orifice within the bladder; (iv) conjoined double ureters (incomplete *pyelon duplex* or bifid ureter, in which the common orifice is in the normal or orthotopic position).

Stephens (Stephens, 1956) points out that in double ureters reflux often takes place, and this would seem to be the explanation of recurrent pyuria in these children.

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on August 29, 1957.

Moreover, he points out that the reflux is just as likely or more likely to occur up the proto-pyelon. Here again Stephens has had success with multiple micturition.

In external ureteric ectopia, obviously another factor is at work — namely, the common stenosis at the ureterocutaneous junction producing dilatation of the whole deutero-pyelon. Here an organic obstruction can be demonstrated and the symptoms corrected by heminephrectomy.

Renal Hypoplasia.

Renal hypoplasia (usually unilateral) is of interest in often presenting both pyelographic and histological findings related to, if not indistinguishable from, those of advanced chronic pyelonephritis. The hypoplastic kidney is often the seat of recurrent acute episodes of pyelonephritis, and gives some support to the attractive suggestion of Marshall (Marshall, 1953) that the kidneys of children who show evidence of acute pyelonephritis contain areas of congenital dysplasia, so that what may be an apparently normal kidney is really a kidney with points of less resistance in it due to histologically demonstrable congenital anomaly.

Tuberculosis.

Tuberculosis is, of course, a rarity in the child's genito-urinary tract, but is not unknown in Australia. Colby gives interesting figures from a sanatorium in Massachusetts; he states that 70% of renal tuberculosis occurs between the ages of 21 and 50 years, 55% between the ages of 21 and 40 years, and 2·2% occurs under the age of 16 years. As in adults, the presence of sterile pyuria etc. merits special efforts to demonstrate or exclude tuberculous infection.

Comment.

Although recurrent pyuria in children, as in adults, demands complete investigation — i.e., microscopic examination of the urine and excretion urography in all cases (with special studies such as cysto-urethrography, cystoscopy and retrograde pyelography in selected cases), we must own that the majority of patients presenting with recurrent pyuria (particularly females) have an apparently completely normal urinary tract. Rarely urethral stenosis is demonstrated, and the patient has no further attacks after dilatation; but this is not common, and we have to suppose some deficiency of the immunological barrier in the prepubertal female urethra.

Treatment with chemotherapeutic and antibiotic agents in such a "normal" tract can be regarded as either curative or "suppressive". If after appropriate attempts at curative therapy we fail, then we must fall back on the use of sulphonamides and other chemotherapeutic or antibiotic agents as a "suppressive". This is a perfectly safe régime when modern sulphonamides are used, and a very effective approach, so long as such therapy is used intelligently, and not merely given in an attempt to relieve, for example, frequency of micturition when there is no question of infection.

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RECURRENT PYURIA.[1]

By A. R. TINK,
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THE title given us for discussion tonight has been carefully chosen, and a few moments spent in consideration of the words "recurrent pyuria" will bring out a theme I wish to develop during this paper.

This term is frequently used in the consideration of a patient in whom we have previously found a urinary infection. After some weeks or months there is a further clinical attack, perhaps precipitated by a respiratory infection. The urine is examined again, pyuria is detected, and so it is said this particular child has recurrent pyuria. Now my point is this: in this use of the word "recurrent" the number of recurrences is proportional in many cases to the diligence with which an adequate examination of the urine is carried out. This word tends to create an impression of isolated episodes of infection, and does not help us to dwell on what may be happening to the kidneys between these attacks. To keep this principle in mind, I believe that it is more helpful to think in terms of chronic, but intermittent, pyuria or bacilluria with or without overt clinical relapses.

It is granted that a large percentage of urinary tract infections in childhood are acute and transient and will settle rapidly without difficulty, never to recur. It is in those cases in which there is persisting infection that a challenge is offered.

In the approach to this problem I should like to stress certain aspects of the clinical features of urinary tract infections in childhood. We are all aware of the classical manifestations of acute infection, especially in older children presenting with high fever, rigors, loin pain and symptoms of bladder irritation. It is not so well known that in neonates and infants these signs may be completely absent, and the child may be merely irritable, fretful and not thriving. It is also noteworthy that urinary tract infection in the newborn male is as frequent as in the female. Chronic urinary tract infection is a common cause of unexplained dehydration in infants. This finding, together with irritability and failure to thrive, is a common triad in this age group.

Let me stress the importance of a proper examination of the urine of any child who is presented with these non-specific symptoms for which no adequate cause can be found. Nesbit and Baum (1955) state that it is of great concern that in about 30% of cases of chronic pyelonephritis there is no preceding violent systemic reaction, and therefore they may escape the notice of both physician and patient.

Physical examination may reveal no abnormality; but, depending on the length of the illness and the degree of damage to the renal tracts, we may find poor development, dwarfing, anæmia, ocular changes and elevation of blood pressure.

An examination of the genitalia for anomalies of development is important. Campbell (1955) states that about one-third of patients with external genital malformation also have upper urinary tract anomalies. A search for meatal stenosis, meatal ulcer or tight phimosis may be rewarding.

Abdominal palpation may reveal hydronephrotic kidneys or bladder distension after micturition indicating residual urine. Rectal examination may reveal relaxation of the anal sphincter, together with an atonic rectum. This is suggestive of a lesion of the lumbo-sacral segment, and may be associated with aberration of tone in the vesical sphincters.

In the consideration of persisting pyuria after an acute attack has failed to respond to therapy, or in chronic cases, a full examination of the urinary tract should be carried out to exclude causes of urinary stasis.

Of the many causes of urinary stasis I should like to comment on four.

1. Congenital valves in the posterior part of the urethra, especially in the male, are important as a cause of obstruc-

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on August 29, 1957.

tion and persisting infection. These are usually not detected on routine instrumentation and are diagnosed only by the findings in a cystogram taken during micturition. If the condition is undetected, urinary back pressure increases, and in time the picture of urinary tract decompensation becomes manifest. The only clinical evidence of these valves may be poor urinary stream and intermittent urinary infection. For a time the bladder compensates, but sooner or later the ureterovesical valves become incompetent, and reflux occurs and leads to irreparable damage to the renal parenchyma.

2. The overloaded colon in the terminal reservoir type of constipation may produce pressure on the urinary tracts. Infection persists until the function of the colon is improved.

3. I should like the urologists present to comment on the frequent diagnosis of urethral stenosis and accompanying cystitis made by them in young females. Often, repeated dilatation of the urethra is carried out on these children. I am unable to understand the frequency with which this is done and rather suspect that the cystitis represents a truly recurrent infection with coliform organisms from the bowel. This appears to be related to the short urethra in the female and poor hygiene.

4. Recently Swenson and Fisher (1955) reported on the association of megacolon and megaloureter due to a defect in parasympathetic innervation. They point out that we find cases of Hirschsprung's disease with and without bladder involvement, and it would be reasonable to search for those with bladder involvement alone. He has found a series of such cases. Of 60 patients with megaloureter, half were found to have a parasympathetic defect of the bladder. Aganglionic megacolon was associated with one-fifth of the defective bladders. Mechanical obstructions such as posterior urethral valves or ureterocele, caused only 10% of megaloureters in this series. Swenson points out that the main defect is lack of adequate detrusor activity in the bladder, as detected by the cystometrogram. Ureteral dilatation is secondary.

In the consideration of adequate investigation of a case of urinary tract infection, the following points are of importance.

The first is examination of the urine. For males a clean specimen collected in a sterile test tube is satisfactory. For females a catheter specimen is essential for bacteriological diagnosis. Later, a method of compromise will be discussed for use in long-term follow up. The specimen should be examined as soon as possible after being passed.

Gram staining of unsedimentated urine is helpful in determining the presence of organisms. It is of value in differentiating infection from probable contamination. It also permits a more informed guess as to the type of organism present, and allows institution of therapy on a more rational basis before the results of culture are available.

Culture of all urine irrespective of the presence of pus cells is essential to detect the presence of organisms and to estimate their sensitivities. As Brainerd (1957) states:

> The presence of pyuria signifies an active lesion infiltrated with leucocytes. During the chronic phase of pyelonephritis pyuria may be absent or insignificant, perhaps for long periods, and the most important diagnostic maneuver involves demonstration of the infecting bacteria. In patients and experimental animals intermittent bacilluria has been noted for extensive periods, the organism sequestering itself in the urinary tract between attacks and appearing only from time to time.

Campbell states that three to five leucocytes per low-power field in the uncentrifuged specimen are within normal limits. At the Royal Alexandra Hospital for Children centrifuged specimens of definite volume are examined with the high power of the microscope, and the results correlate well with Campbell's standard. Casts consisting of leucocytes indicate definite pyelonephritis.

The specific gravity of the urine should always be measured, as it is reassuring to find a value in excess of 1010 in a random sample.

If, in spite of adequate therapy, based on bacteriological information, pyuria or bacilluria persists from an acute attack, or if a child has a second episode, full investigation of the urinary tract should be undertaken. Such investigation should include the following: (i) estimation of the blood urea content; (ii) estimation of renal function, with concentration and dilution tests; (iii) X-ray examination of the abdomen and excretion pyelography; (iv) catheterization after micturition to determine the presence of residual urine; (v) cystography to determine the size and configuration of the bladder and the presence of vesicoureteral reflux, and especially the cystogram during micturition to detect posterior urethral valves; (vi) instrumental investigation by a competent urologist, with special reference to retrograde pyelography and studies on urine from each kidney; (vii) in some cases, cystometric studies.

In spite of full investigation, however, there is a considerable number of cases in which infection persists, and no gross anatomical or neurological lesion can be detected by presently available methods. These cases constitute a great problem, and frequently the results of treatment are poor. There are several factors which seem to contribute to these therapeutic failures, as follows:

1. The general resistance of the patient. Chronic debilitating diseases of other systems make urinary infections difficult to control.

2. The emergence of organisms resistant to the commonly used antibacterial agents, and the increasing incidence of infections caused by staphylococci, *Aerobacter aerogenes* and members of the Proteus and Pseudomonas groups.

3. The duration of infection before treatment is started. This is important, especially in those cases in which symptoms are minimal, as chronicity may already be established prior to therapy. Lesions producing stasis may already reside in the kidney, removed from detection by our various diagnostic endeavours. Hence the importance of bacteriological examination of the urine in the paediatric age group.

4. The frequent use of suboptimal therapy. This seems to be a potent cause of continuing infection leading to chronicity. When all patients with urinary infection are regarded as having actual or potential suppurative interstitial nephritis, and drugs are given in a dosage to produce adequate blood levels to deal with a parenchymal infection, the incidence of urinary infection progressing to chronicity will diminish.

Suboptimal therapy usually produces rapid resolution of symptoms with temporary clearance of organisms from the urine, but does not eradicate the parenchymal infection. A similar situation exists with infections elsewhere in the body, notably staphylococcal pneumonia. If our initial therapeutic attempts are successful in respect of choice of drug and its dosage, rapid resolution as a rule takes place. If not, frequently one is left with a prolonged struggle between the basic defences of the patient and the development of resistant organisms in the infection. Such a struggle may last for weeks or months, and seems to be little influenced by various antibiotics subsequently exhibited.

The casual approach—that two or three sulphadiazine tablets per day and a bottle of *Mistura Potassii Citratis* represent adequate therapy for urinary tract infections—must be abandoned. The real potential for continuing infection must be realized.

The early and intense treatment of the first acute attack is the keynote in preventing chronicity. Full therapeutic doses of the chosen drug or combination of drugs should be given as for any other serious infection for a minimum period of 10 to 14 days.

Opinion is divided on the course to be adopted and the requirements of maintenance therapy. Theoretically, if the urine can be examined bacteriologically at frequent enough intervals and remains sterile, maintenance therapy is not indicated. In practice, however, because intermittent bacilluria may be missed, it would seem wiser to give a smaller maintenance dose for several weeks. Stansfeld and Webb (1954) have proposed that minimum duration of therapy, in any case, should be eight weeks, and in cases in which the symptoms have been present for more than two months it should be prolonged for at least six months. This lengthening of duration of treatment is supported by other observers.

The only criterion of cure is the continuing absence of organisms in the urine over months or years, and the follow up of these children should be correspondingly long.

The obtaining of satisfactory specimens of urine from males is not too difficult, once the necessity for such follow-up examination is explained to the parents. A real problem exists with females, in whom repeated catheterization is objectionable and not without danger unless properly performed.

Kass (1955) has stated that "for practical purposes a Gram stain of the freshly collected and unsedimented urine will differentiate contamination from infection since organisms are readily found in stained specimens of urine when about 10^6 bacteria or more per ml. are present". It may be that routine Gram staining of urine that has remained in the bladder for four hours or more will obviate the necessity for follow-up catheterization in a number of cases. The bladders of patients in whose urine organisms are present should then be catheterized and the urine examined in the usual way. At present, however, and until this method has been further evaluated, it is difficult to escape the conclusion that catheterization of the bladder in the female is indicated for adequate follow-up examination.

The plea that facilities for proper examination of the urine and the performance of excretory pyelography do not exist, or are too expensive, is not good enough. These facilities are available for the vast majority of cases, and not to take advantage of them is to do a disservice to the patient.

Pyelonephritis represents a challenge to general practitioners, pædiatricians and urologists alike, to attack and prevent the considerable morbidity and mortality of this disease. It is only by conscientious application of attention to detail, proper investigation and follow-up examination that this may be achieved. Perhaps if the synonym "interstitial suppurative nephritis, with or without obstruction" is used, it may help to remind us of the seriousness of this disease, rather than regarding it merely as "a chill in the bladder".

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Reports of Cases.

HEREDITARY SPHEROCYTOSIS IN PREGNANCY: REPORT OF A CASE.

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HEREDITARY SPHEROCYTOSIS was first recognized towards the end of the nineteenth century, and since that time, cases have been recorded in which many members of the one family were affected. The most notable and for a long time unappreciated contribution was that of Vanlair and Masius in 1871 under the title of *"la microcythémie"*.

In 1890, Wilson presented a description of six cases in one family, in what is now accepted as a classical summary of the established disease—namely, "a condition in which an enlarged spleen, accompanied by a sallow or subicteric complexion appears as an hereditary condition". It was left to Wilson and Stanley in 1893 only to add anæmia as an important feature, to complete the clinical picture.

Clinical Record.

A Norwegian woman, aged 34 years, booked into the ante-natal clinic at her thirty-second week of pregnancy on July 30, 1957. On general examination she was found to be very pale with a sallow complexion, and her conjunctivæ were slightly icteric, but the spleen was not palpable. The uterus was enlarged to the size of a 32 weeks' pregnancy. The fœtus was presenting in the left occipito-anterior position, and the fœtal heart sounds were normal. Physical examination failed to reveal any more abnormalities except tachycardia and a soft apical systolic murmur. The urine was clear.

Inquiry into the patient's past history revealed that the pallor had been a feature throughout her life, and in recent years she had developed mild exertional dyspnœa. There were no symptoms suggesting gall-bladder disease. In 1951, in Norway, she had been delivered of a living female infant. A post-partum hæmorrhage occurred, with a loss of 600 cubic centimetres, and she had rigors. Treatment consisted of the intravenous administration of iron. Investigation of the family history reveals very little that is definite, but possibly much by inference. The patient's father, who had been well all his life, suddenly died one year ago of "severe anæmia", with no apparent external hæmorrhage. Her brothers, though well, have always been pale. The patient's daughter, now aged five years, is a pale child, though she looks well. Physical examination revealed no abnormality. The results of hæmatological investigations were as follows: The red cells numbered 4,500,000 per cubic millimetre, the hæmoglobin value was 11·4 grammes *per centum*, and the leucocytes numbered 16,600 per cubic millimetre, 63% being neutrophils, 2% eosinophils, 30% lymphocytes and 5% monocytes. Reticulocytes were 1% of the red cells. Some changes in size and shape were detected in the red cells; platelets were plentiful. The leucocytes were all mature forms. The hæmatocrit reading was 39%, the mean corpuscular volume was 87 cubic μ, the mean corpuscular hæmoglobin was 25 micromicrogrammes and the mean corpuscular hæmoglobin concentration was 29%. Tests for fragility of the red cells showed that hæmolysis commenced in 0·48% saline and was completed in 0·32% saline. The response to the indirect Coombs test was negative.

Investigations on the patient at her first visit gave the following results. The hæmoglobin value was 7·7 grammes *per centum*, and the red cells numbered 2,500,000 per cubic millimetre, 7% being reticulocytes; the white cells numbered 6900 per cubic millimetre, 69% being neutrophils, 1% eosinophils, 25% lymphocytes and 5% monocytes. The hæmatocrit reading was 23%, the mean corpuscular volume was 92 cubic μ, the mean corpuscular hæmoglobin was 31 micromicrogrammes and the mean corpuscular hæmoglobin concentration was 33%. The indirect Coombs test produced a negative result. Tests of red cell fragility were carried out; hæmolysis commenced at 0·56% saline and was complete at 0·36% saline. The red cells showed anisocytosis and polychromasia. Macrocytes, microcytes and spherocytes were present. The leucocytes were all mature forms. Cholecystography revealed no abnormality.

The patient was admitted to hospital and a transfusion of a total of 3·5 litres of packed red cells was given. The hæmoglobin value gradually rose to 13·1 grammes *per centum* and the red cell count to 4,120,000 per cubic millimetre, at which time the reticulocyte count was 1% and the red cell fragility commenced at 0·48% saline and completed at 0·32% saline. A four-hourly temperature chart was maintained, and she was examined in consultation by a surgeon with view to splenectomy after delivery. Arrangements were also made to cope with a possible hæmolytic crisis, it being thought that at such a time Cæsarean section and splenectomy might be necessary.

At the thirty-seventh week labour was induced, and she was delivered normally of a living female infant weighing six pounds nine and a quarter ounces. Hæmatological investigations on the infant gave the following findings.

TABLE I.

Date.	Hæmoglobin Value. (Grammes per Centum.)	Red Blood Cells per Cubic Millimetre.	White Blood Cells per Cubic Millimetre.	Reticulocytes per Centum.	Hæmatocrit Reading. (per Centum.)	Mean Corpuscular Volume. (Cubic μ).	Mean Corpuscular Hæmoglobin (μγ).	Mean Corpuscular Hæmoglobin Concentration (per Centum).	Red Cell Fragility (Saline)		Serum Bilirubin Content. (Milligrammes per 100 Millilitres.)
									Hæmolysis Commenced. (per Centum.	Hæmolysis Completed. (per Centum)	
30.7.57	7·7	2,500,000	6900	7·0	23·0	92	31	33·0	0·56	0·36	—
Transfusions.											
2.9.57	12·5	—	—	—	—	—	—	—	—	—	0·4
Confinement.											
9.9.57	13·1	4,120,000	—	1·0	—	—	—	—	0·48	0·32	—
13.9.57	13·7	4,360,000	—	—	—	—	—	—	0·48	0·32	0·4
Splenectomy.											
14.9.57	14·8	4,250,000	—	—	—	—	—	—	0·48	0·32	0·4
16.9.57	14·8	4,200,000	—	—	—	—	—	—	—	—	0·4
18.9.57	—	—	—	1·0	—	—	—	—	0·52	0·32	0·3
20.9.57	13·7	4,160,000	—	—	—	—	—	—	0·48	0·34	0·2
23.9.57	13·9	4,500,000	—	1·0	—	—	—	—	0·48	0·34	—

The serum bilirubin content was one milligramme per 100 millilitres, the hæmoglobin value was 18·8 grammes *per centum*, and the red cells numbered 5,790,000 per cubic millimetre, less than 1% being reticulocytes. The red cells showed some change in size and shape; no spherocytes were seen. Coombs's test produced a negative result. Tests of red cell fragility showed that hæmolysis commenced at 0·44% saline and was completed at 0·32% saline. The infant progressed normally, and on being discharged from hospital on the nineteenth day, the hæmatological findings were as follows: the hæmoglobin value was 18 grammes *per centum* and the red cells numbered 5,500,000 per cubic millimetre, less than 1% being reticulocytes. A blood film appeared normal.

The mother's hæmoglobin level two days after delivery was 13·1 grammes *per centum*.

On September 13, eight days after delivery, splenectomy was performed. The spleen weighed 285 grammes, not including about 1·0 to 1·5 pints of blood lost through a tear in the spleen during operation. Examination of sections of the spleen revealed congestion, large areas of hæmorrhage and pigmentation consistent with a diagnosis of congenital spherocytosis.

Table I summarizes the results of the investigations carried out before, during and after operation. Immediately after operation, the platelet count was 330,000 per cubic millimetre; it rose to 540,000 per cubic millimetre in six days.

Thus there occurred a fall in the reticulocyte count, a rise in the hæmoglobin value, a fall in the serum bilirubin level and a decrease in red cell fragility, which had temporarily risen immediately after operation.

Discussion.

The clinical features of the case presented follow fairly closely the accepted classical features described in the standard texts, except for the rather low serum bilirubin levels and the equivocally impalpable spleen. The low bilirubin level may account for the absence of gall-stones. However, Gänssler *et alii* (1925) described three main types of hereditary spherocytosis, as follows: (i) the complete form; (ii) the "compensated" form, in which 25% of the patients are not anæmic, 40% are without jaundice, 30% are without splenomegaly and 10% are without increased fragility of the red cells; (iii) the mild form, which they referred to as the *leichte hämolytische Konstitution* — that is, normal health with slight increased anisocytosis and minor fragility changes, but no anæmia or splenomegaly. Also, Young *et alii*, in 1951, described six out of 29 cases in which splenomegaly was absent.

When the investigations carried out were compared with those reported by Doan, Curtis and Wiseman, in 1953, and by Sharpe, McLaughlin and Cunningham, in 1939, a drop in the red cell count was found immediately after operation followed by a gradual rise together with a rise in red cell fragility, which returned to the "normal" pre-operative level by the sixth day after operation, a fall in the reticulocyte count and a drop in the plasma bilirubin level (*vide supra*). The blood transfusions were unaccompanied by any reactions.

Summary.

A case of hereditary spherocytosis, presenting for the first time in a pregnant woman whose spleen was not palpable, is described.

Treatment with blood transfusions and splenectomy was successful after a normal confinement. Her two children have at the moment normal hæmatological findings.

Acknowledgements.

I wish to thank Dr. R. H. Higham, Honorary Obstetrician and Gynæcologist, for permission to publish this case, and Dr. Marjorie Thomas and her staff for their help in the various investigations.

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PERFORATION OF MECKEL'S DIVERTICULUM BY GRAPE SEEDS.

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FOREIGN-BODY PERFORATION of a Meckel's diverticulum is a rare occurrence. Only 28 cases are found in a survey of the literature dating back to 1899 (Alhadeff, 1955; Rawlinson, 1956). Of these 17 were perforations by fishbones, five by wood splinters and four by needles or pins. Soft, blunt objects have also been recorded as causing perforation of a Meckel's diverticulum—cabbage stalk (MacFarlane, 1948) and rolled tomato skin (Ward-McQuaid, 1950). There does not appear to be any record of perforation of a Meckel's diverticulum by grape seeds, although Du Toit (1925) has reported impaction of prickly

pear seeds in a Meckel's diverticulum and in the adjoining ileum causing intestinal obstruction.

Clinical Record.

The patient was an Italian male fruit-shop proprietor, aged 41 years. He presented with a history of moderately severe pain of 24 hours' duration in the region of the umbilicus. Prior to the onset of pain the patient had been in perfect health. The pain was at times colicky in nature and was increasing in severity. It was persistenly around the umbilicus, the patient indicating one inch below and to the right of the umbilicus as the point of maximum intensity of pain. There had been no vomiting or diarrhœa, although the patient had not been able to eat his luncheon because of nausea and anorexia. The bowels had been normally opened. The patient had never passed blood *per rectum*. He had had no previous indigestion or abdominal pain. There were no symptoms referable to any other system. There was nothing relevant in his previous or family history or in his personal habits. The patient had not had any previous operations.

On examination, the patient was a well-developed adult male in no obvious distress. The temperature was 100°F., the pulse rate was 84 per minute and regular; respirations numbered 18 per minute. The tongue was furred. On examination of the abdomen, moderate tenderness and guarding were elicited on deep pressure just to the right of and below the umbilicus. There were no other areas of tenderness or guarding. No abdominal masses were felt. The hernial orifices were normal. Examination *per rectum* revealed no abnormality. The bowel sounds were normal. There was no abdominal distension. The urine contained no sugar, albumin or bile. Examination of the other systems revealed no abnormal findings.

As the diagnosis was thought to be other than acute appendicitis, the abdomen was opened by a right lower paramedian incision. A mass measuring about three inches in diameter was discovered, adherent to the anterior parietal peritoneum at the level of the umbilicus. The greater omentum was wrapped around the mass and adherent to it. Also adherent to the mass were several loops of small intestine. On clearing away the adherent small intestine and greater omentum, a small abscess was opened into, and it became obvious that the mass consisted of a Meckel's diverticulum, approximately two and a half feet from the ileo-caecal valve, a recent perforation of which had resulted in localized peritonitis and abscess formation.

The diverticulum was removed by ligating its small mesentery and then excising the diverticulum at its base. The ileum was closed transversely to its long axis by two rows of sutures. The vermiform appendix, which appeared normal, was removed. There was no evidence of mesenteric adenitis. In spite of a heavy wound infection, the patient made a comfortable and speedy recovery. Twelve months after the operation he was in excellent health.

Examination of sections of the specimen removed at operation revealed the findings described in the pathologist's report (*vide infra*) and seen in the photographs (Figures I, IIA and IIB) with the exception that the foreign material in the diverticulum was absolutely tightly packed. (The loosely-packed appearance in Figure IIA and IIB is due to the fact that much of the foreign material was lost in the preparation of the specimen.)

Two grape seeds were impacted in the small perforation in the globular portion of the Meckel's diverticulum. On subsequent questioning, the patient stated that he had not eaten grapes for at least four months prior to the operation (grapes having been "out of season" for some months).

Pathologist's Report.

The pathologist's report was as follows:

> The specimen was a pyriform piece of small intestine 6 centimetres by 4·5 centimetres by 4 centimetres with a lumen only at one end. It was identified as a Meckel's diverticulum arising from the antemesenteric border of the ileum about 75 centimetres from the ileocaecal valve.
>
> A fissure separated the specimen into two parts. The proximal (2 centimetres long) showed the gross appearance of small intestine. The distal part was a roughly globular, firm nodule 4 centimetres in diameter with a smooth, glistening peritoneal surface, and pale fibrous tissue was visible through it. Rough fibrous tags were also present on one side. Situated 1·5 centimetres distal to the fissure there was a perforation 0·3 centimetre in diameter. The cut surface showed a narrow communication 0·6 centimetre wide between the proximal and distal parts. The wall of the distal segment was thick and firm and the lumen was filled with inspissated fæcal material including various seeds, vegetable fibres and short sticks.
>
> Microscopical examination of the proximal segment shows small intestine with a mild to moderate grade of chronic inflammation and fibrosis chiefly in the submucosa. Sections of the distal segment also show the general structure of small intestine. There is marked chronic inflammation including lymphoid follicles in the mucous membrane. The subserosa shows notable inflammatory fibrosis which produces the opaque appearance seen in the gross specimen.
>
> In one area of the distal segment the mucous membrane is intermediate in structure between small and large intestine.
>
> No gastric mucosa has been found. In the region of the perforation the mucosa has desquamated.

FIGURE I.

Meckel's diverticulum, showing the expanded, glistening, thickened distal portion. The perforation may be seen below the centre of the expanded segment.

Discussion.

Bowel contents can usually pass in and out of a Meckel's diverticulum, because the diverticulum has in most cases a wide connexion with the ileum. (In this patient the lumen of the diverticulum was equal in diameter to the lumen of the ileum.) However, ulceration and inflammation may cause fibrosis and constriction of the diverticulum at any point of its length, and foreign bodies may be entrapped, having been pushed into the diverticulum by peristalsis and the onward passage of the intestinal contents, but cannot pass out of the diverticulum.

Sharp foreign bodies in a Meckel's diverticulum will cause perforation or hæmorrhage, whereas multiple smooth foreign bodies will cause inflammation, ulceration and peritonitis; or by the weight of the entrapped foreign material a pedicle may form by stretching, resulting in torsion or obstruction and strangulation of the intestine (Leighton John, 1955).

In this case it appears that a Meckel's diverticulum of large lumen existed. The constant passage of foreign bodies (seeds, sticks and vegetable fibres) in and out of it caused ulceration, inflammation and stricture formation towards the middle of the diverticulum. The various foreign bodies were then entrapped in the distal half of the diverticulum, and as more and more foreign matter was pushed into this section of the diverticulum, it became stretched and elongated, giving rise to the globular appearance seen in the photographs. The wall of this portion of the diverticulum became subject to recurrent inflammatory changes and thickened by fibrosis. The pressure of so many foreign bodies so tightly packed caused eventual ulceration, pressure necrosis and gradual perforation in one small

area. Very little soiling of the peritoneum occurred, as the greater omentum would have already been wrapped around the diverticulum because of the recurrent mild inflammatory reactions. These adhesions to the greater omentum and to the parietal peritoneum would have also prevented torsion and strangulation of the small bowel.

Similar cases have been reported by Miller (1927), who described a case in which impacted tomato and grape seeds in a Meckel's diverticulum had formed a cyst eventually resulting in small-bowel strangulation, and by Du Toit (1927), who reported a case in which prickly pear pips were incarcerated in a Meckel's diverticulum, causing stretching with pedicle formation; this resulted in snaring of the bowel and small gut obstruction.

Although sudden and very severe symptoms of perforation can occur, as reported by Alhadeff (1955), in this case, as in the majority of foreign-body perforations of a Meckel's diverticulum, the perforation took place silently, the onset of moderate pain was gradual and the symptoms and signs of peritonitis were slight. The reason for the gradual perforation of the Meckel's diverticulum in this case has already been outlined, and it would appear that this is the usual sequence of events in practically all

FIGURE II.

A, longitudinal section of the Meckel's diverticulum; B, sagittal section of the expanded distal portion of the Meckel's diverticulum, showing multiple foreign bodies; much of the foreign material was lost during the preparation of the specimen.

cases of perforation of a Meckel's diverticulum by blunt or round foreign bodies. Perforation of a Meckel's diverticulum by sharp foreign bodies is more likely to present as an acute abdominal emergency.

In this case the site of pain and tenderness was characteristically situated at and just below and to the right of the umbilicus.

The diagnosis of a diseased Meckel's diverticulum is always very difficult and is practically always made at operation.

A routine search for a Meckel's diverticulum during abdominal operations should be made, especially when the operation is for suspected appendicitis and no obvious lesion can be found to account for the symptoms. The terminal six feet of the ileum should be inspected in searching for a Meckel's diverticulum. If one is found, it should be removed if possible, even though it may appear normal. The diverticulum should be excised at its base, as heterotopic tissue, if present, is usually found at the base.

Summary.

A case of perforation of a Meckel's diverticulum by grape seeds is reported.

Perforation of a Meckel's diverticulum by foreign bodies is rare, and is mostly due to sharp objects, such as fish bones and needles.

Pre-operative diagnosis of Meckel's diverticulum disease is most difficult, but the importance of pain and tenderness at and just to the right of the umbilicus in these cases is stressed. The umbilicus may be the only tender spot in the abdomen.

Whereas sharp objects may cause perforation of a Meckel's diverticulum, which presents as an acute abdominal emergency, blunt or rounded objects generally cause a silent perforation, with intermittent abdominal pain and minimal signs of peritonitis.

The hold-up of the passage of a foreign body through the small intestine should bring to mind the possibility of its being entrapped in a Meckel's diverticulum (Leighton John).

The importance of a routine search for a Meckel's diverticulum and its removal when one is found during abdominal operations is stressed. The terminal six feet of the ileum should be inspected when searching for a Meckel's diverticulum.

Acknowledgements.

I wish to thank Dr. E. Hirst, pathologist at the Kanematsu Memorial Institute of Pathology, Sydney Hospital, for the pathological report and Mr. R. Money, Department of Photography, Sydney Hospital, for the photographs.

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ACCIDENTAL INOCULATION TUBERCULOSIS.

By F. E. HEYMANSON,

State Tuberculosis Physician, Perth, Western Australia,

AND

H. R. ELPHICK,

Medical Superintendent, State Sanatorium, Wooroloo, Western Australia.

Clinical Record.

A LABORATORY TECHNICIAN, A., aged 23 years, reported on September 19, 1596, that five days previously he had dropped a hypodermic syringe and needle containing a suspension of *Mycobacterium tuberculosis*. The needle caught in his trouser leg in falling, but so far as he was aware at that time, did not penetrate or even touch his skin. Immediately after the accident the skin and adjacent trouser leg were swabbed with absolute alcohol.

On the day when A. reported, there was on the medial aspect of the right thigh an ill-defined swelling some 30 millimetres in diameter, through which could be palpated a deeper nodule five or six millimetres in diameter. At the apex of the larger swelling there was a minute red spot, but otherwise reddening was not apparent. The lesion was a little tender.

In view of the doubt as to whether or not the lesion actually represented inoculation tuberculosis, intramuscular penicillin treatment was instituted over a period of five days, but was without effect, and there may have been slight increase in the swelling over this period.

On September 27 the swelling was opened, hyperæmic and œdematous subcutaneous tissue being revealed portion of which was excised. Immediately after this procedure the administration of streptomycin, isoniazid and "Terramycin" was begun. Direct examination of the specimen revealed typical acid-fast organisms, and culture and guinea-pig inoculation both gave positive results. Histological examination of sections revealed a small patch of necrosis with thickening of the epidermis, which was partly infiltrated with polymorphs and lymphocytes.

The patient was transferred to Wooroloo Sanatorium on September 29 when his wound appeared healthy. On October 5, when the sutures were removed, a small central slough was noted, and from this area a small amount of pus discharged persistently during the next few weeks. The wound was dressed with streptomycin powder and "Vaseline" gauze, and later with eusol compresses, and on November 15 pus from the sinus produced a typical culture of acid-fast and alcohol-fast bacilli on Löwenstein-Jensen medium.

On December 8 the wound was probed, and a shallow undermined ulcer was found to extend subcutaneously with a radius of one centimetre from the small central orifice; on December 14 the ulcer was demonstrated radiologically after the instillation of "Dionosil". On December 20 the skin edges were therefore excised and the ulcer was laid open and packed with "Vaseline" gauze, after insufflation with streptomycin powder. After this procedure steady improvement occurred, and the patient was discharged from the sanatorium on January 31, 1957, by which time the ulcer was filled with healthy granulation tissue and the epithelium was advancing quite rapidly from the edges. Histological examination of sections of the excised skin and wall of the indolent ulcer revealed a picture of tuberculosis; there was an area of central necrosis surrounded by granulation tissue with giant cells of the Langhan's type and fairly typical tubercle formation.

The patient continued his dressings at home, but was readmitted to the sanatorium on February 27 because of the persistence of a small central area of ulceration. This was dressed with a 1/400 aqueous solution of "Zephiran" and firm pressure was applied, and on March 8 the wound had completely healed.

Chemotherapy after his admission to the sanatorium consisted of the daily administration of streptomycin, one gramme, and isoniazid, 300 milligrammes, from September 29 to December 6, 1956, when P.A.S., 12 grammes per day, was added. The combination of three drugs was continued until the patient's discharge from hospital on March 8, 1957, when streptomycin was discontinued, and he was advised to continue P.A.S. and isoniazid for a further period of at least six months.

The culture of tubercle bacilli apparently responsible for the accidental inoculation, when subcultured and investigated for sensitivity to antibiotics, was found to be resistant to 100 microgrammes of streptomycin, 100 microgrammes of P.A.S. and 200 microgrammes of isoniazid per cubic centimetre of culture medium. The organisms cultured from the discharge on November 15, 1956, were similarly investigated and found to be resistant to 20 microgrammes of streptomycin and 200 microgrammes of isoniazid per cubic centimetre of medium, but completely sensitive to P.A.S. However, in spite of the apparent resistance of the organisms to chemotherapeutic agents, progressive healing occurred after the excision of the skin edges from the undermined subcutaneous ulcer.

Comment.

This case represents a typical example of reinfection tuberculosis of the skin occurring in a subject with a known positive Mantoux reaction. There was no regional glandular involvement, as was to be expected, although this is known occasionally to occur, even when the Mantoux reaction is positive (Grady, 1951).

Reference.

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Reviews.

Clinical Gastroenterology. By Eddy D. Palmer, M.D., F.A.C.P.; 1957. New York: Paul B. Hoeber. 10" × 7", pp. 640, with 216 illustrations. Price: $18.50.

THIS book satisfies a need for those who seek a modern survey of diseases of the digestive system beyond the compass of standard text-books of medicine, without undue complexity.

The emphasis is twofold, on conditions in which advances in knowledge have occurred, and on conditions which are uncommon but not rare. The sections are designed to be read rather than consulted; no references are included in the text, which makes for clarity of presentation, but detracts from the value of the book. As the author states in his preface, the approach is primarily clinical; theoretical and experimental considerations are therefore eschewed. The result is a series of essays on a wide range of subjects, rather than a comprehensive outline. For the most part these are well balanced, and the information is well integrated. Naturally there is some uneveneness of quality. Chapters on the stomach, duodenum, pancreas, colon, portal hypertension and gastro-intestinal bleeding are excellent. In view of the author's interests, the sections on the œsophagus, cardia and diaphragm are curiously disappointing. The chapter on gastro-intestinal manifestations of other diseases is all too brief, and although the psychosomatic approach is well integrated in an introductory chapter and throughout the text, the book lacks a section on the assessment of symptoms, and little mention is made of differential diagnosis.

From the pen of an internist the sections on treatment are happily brief and pithy; the author is more concerned with what can be expected from surgery, although the nihilistic approach to gastric carcinoma is at variance with his avowal that statistics should not necessarily be applied to individual patients. No special diets are advised. The treatment of amœbiasis is poorly dealt with, and not all would agree with the advice that cholecystectomy should be performed for acute cholecystitis. Some recent advances, notably the new knowledge on bilirubin and penicillamine for Wilson's disease, are not included. Many new laboratory investigations are mentioned without adequate evaluation; but radiological findings are well discussed and illustrated throughout.

The author's conversational style makes for easy reading, enthusiasm is well communicated, and the text abounds with succinct sentences which are arresting, although not without an occasional touch of the sardonic.

The Stress of Life. By Hans Selye, with an introduction by Sir Heneage Ogilvie; 1957. London, New York, Toronto and Melbourne: Longmans, Green and Company. 8½" × 5½", pp. 346. Price: 22s. 6d. (Australian).

DURING the past twenty years Hans Selye has written many thousands of words in his attempts to make clear his theory as to the relation of stress to bodily disorders. A large number of medical men are still unable to understand the theory and its applications. In his latest published work, "The Stress of Life", Hans Selye has attempted to explain his concepts for the non-medical reader. The work is divided into five books, as follows: the discovery of stress (Book I), the dissection of stress or the analysis of its mechanism in health (Book II) and in disease (Book III), sketch for a unified theory (Book IV) and implications and applications (Book V). The work is extremely difficult to read, and indeed the author recommends that the lay reader should start with Book V, then Book I, the summaries only of Books II and IV and then Book III. Besides being very difficult to follow, it is also very trying, for there is much about the author himself which is largely irrelevant. The meaning of the idea of stress is dealt with at great length, and a variety of definitions are given. What is said to be a precise definition which will fit all the facts is as follows: "Stress is a state manifested by a specific syndrome which consists of all the non-specifically induced changes within a

biological system." It would seem that stress can be set up by any external stimulus. Another statement is as follows: "Stress is defined as the state which manifests itself by the G.A.S. The latter comprises adrenal stimulation, shrinkage of lymphatic organs, gastrointestinal ulcers, loss of body weight, alterations in the chemical composition of the body and so forth." There is also a local adaptation syndrome (L.A.S.) in local tissues. It takes very concentrated attention in reading to get anything like a clear idea what it is all about. When the application of the stress concept, G.A.S. and L.A.S., to actual disease processes is considered, it appears that only some of the symptoms of the syndrome may appear. If the reader has been able to proceed this far and can accept much of the argument, there is a great deal of interest in Books IV and V, which are largely philosophical. It is difficult to imagine that a non-medical person could read the whole book, and if he did, that he could have any clear ideas on disease processes. For the medical reader, who wishes to learn something of Selye's theories, this is probably the best account available, and while he might be inclined to doubt much in the section on diseases of adaptation, he would find much of interest.

Soldier Surgeon in Malaya. By Thomas Hamilton, Lieutenant-Colonel, E.D., R.A.A.M.C. (ret.); 1957. Sydney, London, Melbourne, Wellington: Angus and Robertson, Limited. 8½" × 5½", pp. 224, with illustrations. Price: 18s: 6d.

THE high merit of the work done by the 2/4th Australian Casualty Clearing Station during the Malayan Campaign is a matter of official record. Nevertheless, Lieutenant-Colonel T. Hamilton's history of his unit's war service provides a welcome and stimulating complement to the official records. It is a personal record, in that it is written in the first person and is confined almost exclusively to the scope of the author's own knowledge and experiences; yet it is not so much his own story as an entertaining and gripping history of his unit, told in a simple, straightforward, and at times breezy narrative that is always well sustained. Even to those who were not there, it must convincingly display the stamp of authenticity. Those who knew the unit in action, the story will impress as full yet restrained, gratefully free from heroics, and true to the least detail; it brings back the very essence of those times. Not only members of the 2/4th Casualty Clearing Station, but all who served in Malaya will find in this book much to stir up memories, while few Australians could fail to find it of absorbing interest.

Notes on Books.

Discovery. Number Two, 1957. Melbourne: University of Melbourne. 9½" × 7", pp. 96, with 80 illustrations. Price: 2s. 6d.

THIS publication is an attempt to introduce the lay reader to selected aspects of research being conducted under the ægis of the University of Melbourne. The medical section is edited by Professor Rubbo. It is a well-presented booklet, and on the cover is an excellent picture in colour of the very striking mural sculpture which dominates the interior of the new Wilson Hall. The individual articles are brief and informative, and the whole is liberally supplied with illustrations of a very high quality. In general it seems well calculated for the purpose for which it is designed, and we hope it will be widely distributed. The first number appeared two years ago.

Experimental Psychopathology. Edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D.; 1957. New York and London: Grune and Stratton. 8½" × 5½", pp. 288, with illustrations, tables and graphs. Price: $6.50.

THESE are the proceedings of the American Psychopathological Association's fourty-fifth annual meeting in New York in June, 1955. Edited by Paul H. Hoch and Joseph Zubin, both of the New York State Psychiatric Institute, they relate to the main experimental currents in the field of psychopathology. They refer to both animals and man, the field ranging from perception of social attitudes to experimental induction of depersonalization. The editors express the hope that a common vocabulary will emerge from the collaboration of clinicians and experimentalists in these matters, and that this will assist the integration of the two fields. The book is well set out, with discussions following particular groups of articles on similar subjects. Many of the articles are illustrated, and there are comprehensive diagrams and graphs.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Die gezielte Diagnostik in der Praxis: Graundlagen und Krankheitshäufigkeit", by Dr. Robert N. Braun, with a foreword by university professor Dr. Hans Schulten; 1957. Stuttgart: Friedrich-Karl Schattauer-Verlag. 9½" × 6½", pp. 196. Price not stated.

A monograph relating to morbidity statistics.

"An Introduction to Functional Anatomy", by David Sinclair, M.A. (Oxford), M.D. (St. Andrews); 1957. Oxford: Blackwell Scientific Publications. 8½" × 5½", pp. 428, with 166 illustrations. Price: 42s. (English).

This book is designed for the use of those in the paramedical services and has been written around the syllabus of the Association of Occupational Therapists.

"The Glaucomas", by H. Saul Sugar, M.D., F.A.C.S.; Second Edition; 1957. New York: Paul B. Hoeber. 9½" × 6", pp. 528, with 164 illustrations. Price: $13.50.

A revised and enlarged edition.

"The Biologic Basis of Cancer Management", by Freddy Homberger, M.D., with forewords by Lauren V. Ackerman, M.D., Clarence Cook Little, Sc.D., and Alton Ochsner, M.D.; 1957. New York: Paul B. Hoeber. 9½" × 6", pp. 376, with 10 illustrations. Price: $10.00.

The author is Research Professor of Medicine at Tufts University School of Medicine.

"Sanitary Science Notes: A Handbook for Students", by H. Hill, F.R.S.H., F.A.P.H.I., A.M.I.P.H.E., and E. Dodsworth, F.R.S.H., M.A.P.H.I., M.Inst.P.C.; Third Edition; 1957. London: H. K. Lewis and Company, Limited. 6½" × 4", pp. 144. Price: 10s. 6d. (English).

The text has been amended and added to.

"Chemotherapy and the Central Nervous System", by Henry McIlwain, Ph.D., D.Sc.; 1957. London: J. and A. Churchill, Limited. 9½" × 6", pp. 336, with 61 illustrations. Price: 45s. (English).

Deals with the development of methods and principles in chemotherapy as a whole, and with the application of chemotherapy to produce drugs for use in the treatment of mental disorders.

"Eden and Holland's Manual of Obstetrics", by Alan Brews, M.D., M.S. (Lond.), M.R.C.P. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G.; Eleventh Edition; 1957. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 764, with 432 illustrations. Price: 63s. (English).

The text has been thoroughly revised.

"How to Use a Medical Library: A Guide for Practitioners, Research Workers and Students", by Leslie T. Morton, A.L.A.; Third Edition; 1957. London: William Heinemann (Medical Books), Limited. 7½" × 4½", pp. 64. Price: 7s. 6d. (English).

The author is Information Officer of the *British Medical Journal* and was formerly Librarian of St. Thomas's Hospital Medical School.

"Tumor Surgery of the Head and Neck", by Robert S. Pollack, M.D., F.A.C.S.; 1957. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 104, with 49 illustrations. Price: 55s.

Intended to bridge the gap between the several specialties involved in this type of surgery.

"Laboratory Applications in Clinical Pediatrics", by Irving J. Wolman, M.D.; 1957. New York, Toronto and London: The Blakiston Division, McGraw-Hill Book Company, Incorporated. 9" × 6", pp. 1032. Price: $15.00.

"Intended for students and residents, for laboratory directors in general hospitals, and particularly for practitioners who are not in close contact with pediatrics teaching centers, it endeavours to condense and discuss those major laboratory phenomena which seem pertinent to the clinical care of infants and children."

The Medical Journal of Australia

SATURDAY, JANUARY 25, 1958.

A NEW MEDICAL SCHOOL FOR NEW SOUTH WALES.

AN important corollary to the publication of the Murray Report, and the acceptance of its principal recommendations by the Commonwealth Government, is the plan to establish a new medical school in New South Wales. The intention of the New South Wales Government, according to a reported announcement[1] by the State Minister for Health, Mr. W. F. Sheahan, is to build another pre-clinical medical school in the Sydney suburb of Kensington. This is to be part of the New South Wales University of Technology, to be renamed the University of New South Wales. Mr. Sheahan expressed the hope that the first students for the new school would be enrolled not later than 1960. An advisory medical committee has been set up to consider the matter under the chairmanship of Dr. Kenneth Starr, who is head of the Cancer Research Institute, Prince of Wales Annexe, Sydney Hospital. Those invited to join the committee are: the Professor of Medicine in the University of Sydney, Professor C. R. B. Blackburn; the Chairman of the New South Wales Faculty of the College of General Practitioners, Dr. W. A. Conolly; the Director of the Kanematsu Memorial Institute of Pathology, Sydney Hospital, Dr. F. C. Courtice; the General Medical Superintendent of the Royal North Shore Hospital of Sydney, Dr. W. Freeborn; the President of the Royal Australasian College of Surgeons, Dr. Douglas Miller; the Vice-Chancellor of the New South Wales University of Technology, Professor J. P. Baxter; a member of the Council of that University, Mr. J. W. Goodsell; the Dean of the Faculty of Medicine in the University of Sydney, Professor B. T. Mayes; Emeritus Professor H. K. Inglis; Dr. C. G. McDonald; Dr. S. Devenish Meares; Dr. P. J. Kenny; Dr. K. Kirkland; Dr. Harold Kramer; Dr. F. Ritchie; Dr. L. T. Shea. Mr. Sheahan is reported to have said that the committee would be asked to make recommendations relating to the order and nature of measures essential to the establishment of the proposed medical school and to the composition of the proposed medical curriculum at the undergraduate, honours and post-graduate levels; it would also be asked to give its views on the financing of teaching hospitals.

The idea of a second medical school in Sydney is not new. Plans have been formulated for some time for the association of a pre-clinical medical school at the New South Wales University of Technology with an independent clinical school at Sydney Hospital. In this regard it is impossible not to notice the strong representation of Sydney Hospital and, to a lesser extent, of St. Vincent's Hospital, on the present committee (and incidentally the inexplicable and regrettable absence of an official representative of the British Medical Association). The plan is probably an inevitable and logical development, precipitated by the statements in the Murray Report which Mr. Sheahan quoted:

> There appears to be every justification for the establishment of a second medical school in New South Wales, where already the University of Sydney is attempting to cope with far greater numbers than the University of Melbourne. . . . If there should be a new medical school, there is much to be said for placing this in the N.S.W. University of Technology.

The Murray Report then goes on:

> This raises the whole question of the future responsibilities of this institution [the University of Technology]. Already it has extended the coverage of its courses from science and engineering and the associated humanities to include Faculties of Architecture and Commerce. . . . If, as appears to us desirable, an upper limit of 12,000 students is anticipated for the University of Sydney, it may in any case be necessary for the N.S.W. University of Technology to relieve the pressure on the University of Sydney in a number of fields. While there should be no need to anticipate duplication of more than a proportion of the courses now provided by the University of Sydney, it must be expected that the N.S.W. University of Technology will assume many of the features of a traditional university. In such an event, it might more appropriately become known as the University of New South Wales. Such a change in title would in any case be desirable were it ever to grant degrees in medicine: such degrees granted by a University of Technology might place their holders under some disability.

The outcome of this was the announcement[1] by the State Minister for Education, Mr. R. J. Heffron, that the New South Wales University of Technology would be renamed the University of New South Wales, and the courses of this university would be extended to include a Faculty of Arts.

This is a most satisfactory development. The name University of Technology has always seemed anomalous, and it would certainly have been undesirable to have it associated with a medical school and medical degrees. Curiously enough, the anomaly was accentuated by the fact that from the inception of the New South Wales University of Technology a serious attempt has been made to ensure that students undertaking technical courses shall have at least a nodding acquaintance with the humanities—something which is lacking at the traditional universities and which might well be copied by them. It is to be hoped that the inauguration of a Faculty of Arts will not interfere with this admirably conceived procedure (whatever its defects may be in practice) and that the students in the new medical school will share in its benefits. As the Murray Report states in its opening chapter, "the world simply cannot afford that its highly specialized professional men, technologists and scientists should not also be fully educated as rounded human beings". While there are real difficulties in doing a great deal towards the fulfilment of this ideal, it would be a mistake to push it aside as wholly impracticable. It will be interesting to see how the University of New South Wales, with its already established policy of encouraging the humanities and now its expansion into traditional university form, will approach the matter.

[1] *The Sydney Morning Herald*, December 19, 1957.

[1] *The Sydney Morning Herald*, January 10, 1958.

This question of broad university education is, of course, the main objection to the system in which the medical school, both pre-clinical and clinical, is centred around a teaching hospital, practically the only real association with a university being that it acts as the examining body and confers the degrees. This is the system in the London hospitals and in many other places in Europe and North America, and it must be admitted that in general it works satisfactorily. It is certainly streamlined, as its supporters point out, but it involves a compromise with expediency that we may well come to regret.

In passing, it is a little mystifying to recall that only two months ago Mr. Sheahan was reported[1] as having said that the Royal North Shore Hospital of Sydney was the proper site for a new pre-clinical medical school, and that the new medical school should be associated with a new university to be built on the north side of the harbour to serve the needs of the "great new city" which had developed there. Perhaps there are going to be three universities and three medical schools in Sydney; although it would not be so without the most vigorous of protests and counter-claims from, amongst other centres, Newcastle and Parramatta.

Current Comment.

DISSEMINATED SCLEROSIS AND THE RUSSIAN VACCINE.

MUCH interest has been aroused by Press and radio reports of a vaccine of Russian origin which has been used in New Zealand and elsewhere for the treatment of disseminated sclerosis. However, all inquiries fail to indicate that the vaccine has any proven value. It is not new and has in fact been on trial for a number of years. Reports submitted to a world conference of neurologists held in Brussels last year gave no grounds for optimism in its use. More recently G. W. A. Dick, Florence McKeown and D. C. Wilson,[2] of the Department of Microbiology at the Queen's University of Belfast, have reported on a laboratory study of the virus from which the vaccine is prepared. They state that the vaccine consists of a formolized suspension of the brains of rats or mice which have been infected with the SV strain of a virus of acute encephalomyelitis of man—*encéphalomyélite humaine aiguë* (E.H.A.). It is manufactured and distributed by the Metchnikoff Institute in Kharkov, where it is called the "vaccine of Margoulis and Choubladze". In 1956 A. Choubladze *et alii* reported that a large percentage of patients suffering from disseminated sclerosis had antibody to E.H.A. virus. This, in conjunction with other virological studies of E.H.A. virus, led them to believe that there was infection with this virus in some cases of disseminated sclerosis. They accordingly used the formolized preparation for the treatment of acute encephalomyelitis and disseminated sclerosis. However, Dick, McKeown and Wilson have been unable to find that sera from patients in Northern Ireland with disseminated sclerosis show any significant neutralization of the SV strain of E.H.A. virus, which appears to be rabies virus. They comment that since they cannot find any relationship between the virus of E.H.A. and disseminated sclerosis in Northern Ireland, and since this virus cannot be distinguished from that of rabies, "there seems to be no rationale for using the 'vaccine of Choubladze and Margoulis' in preference to any other rabies vaccine in the treatment of multiple sclerosis". Moreover, the Russian workers have claimed that the vaccine has produced amelioration in 30% of cases, and that it does not help patients who have been ill for a long time. In view of the well-known fact that spontaneous remissions are common in early cases of this condition and T. J. Putnam's finding that 47·5% of patients given any kind of treatment have been reported to show improvement, the Russian figures have little, if any, significance. In addition to this, as Dick and his colleagues point out, the use of such a vaccine may do harm.

The position seems to be quite well summed up in a letter which was sent on November 20, 1957, by the Vice-President of the Multiple Sclerosis Society of Victoria to the principal daily newspapers in Melbourne. So far as we know, the letter was not published despite its practical importance. The letter is as follows:

> Dear Sir,
>
> To ensure protection of the public in a matter of vital concern, we ask your co-operation in publishing the following, at an early date:
>
> "Last Saturday, 16th November, 1957, several broadcasts over 3AR and 3LO told about a vaccine of Russian origin reported to have cured a New Zealander suffering from Multiple (Disseminated) Sclerosis (MS for short).
>
> "The Multiple Sclerosis Society of Victoria would like to warn the public, and especially patients suffering from above nervous disorder, against pinning their hopes—and spending their money—on any so-called 'cure' that is not recommended by their own doctors.
>
> "One of the aims of this Organization is 'to keep informed about advances in research, diagnosis and treatment of Multiple Sclerosis'. During 1956, my Society was made aware of the Russian claim of having developed a vaccine (Margulis-Shubladze-Solovyov) useful in the treatment of early stages of selected types of MS. Immediately, we sent for, and obtained, information from Russia, as well as from hospitals and bacteriological institutes in England, France, Sweden, Germany and U.S.A. The Swedish reply that—following extensive research—it is 'doubtful and even unlikely that the Russian Multiple Sclerosis Vaccine is of any value' was confirmed by most other investigators abroad, as well as by our own medical specialists in Victoria.
>
> "Further research into cause and control of MS is carried out all over the world in ever-increasing measure, and it is hoped that a cure for this baffling illness will soon be found. Meanwhile, we strongly recommend to MS patients and their relatives, not to embark on expensive courses of treatment without first discussing the matter with their medical advisers.
>
> Yours faithfully,
>
> (Signed) MRS. RUTH SHEFFIELD,
> Vice-President, Multiple Sclerosis
> Society of Victoria.

CHRONIC THYROIDITIS.

IN 1956 R. W. Luxton and R. T. Cooke published a paper[1] on the significance of serum-flocculation reactions in the diagnosis of Hashimoto's disease. In their opening paragraph they stated that there was "still a lack of knowledge of its clinical picture and consequent disagreement about its incidence". They had found the condition not uncommon in their practice, and, maintaining that many patients suffering from it were operated upon unnecessarily, set out to show that accurate diagnosis without surgery was facilitated by the use of serum-flocculation tests. The abnormal reactions to these tests found in this condition indicated raised serum gamma-globulin levels. At the same time Professor E. Witebsky and his co-workers had been studying the serological reactions to thyroid extract in animals, and had succeeded in producing specific thyroid antibodies in rabbits inoculated with extracts of their own thyroid glands. These antibodies caused a destructive reaction in the remaining thyroid tissue of the sensitized animals. There is strong evidence that the substance exciting this antigenic reaction is thyroglobulin, a protein specific for the thyroid gland.

[1] *The Sydney Morning Herald*, October 26, 1957.

[2] Brit. M. J., 1958, 1: 7 (January 4).

[1] *Lancet*, 1956, 2: 105 (July 21).

The next contribution to the discussion came from I. M. Roitt and his co-workers,[1] who suggested that Hashimoto's disease might be caused by an immune response by the individual against his own thyroid tissues. In support of this hypothesis they were able to show that the serum of patients with Hashimoto's goitre gave precipitins when tested against extracts of both normal and thyrotoxic human thyroid tissue, and that the antibodies involved were organ-specific to thyroid gland. They concluded that patients with Hashimoto's disease were immunized against human thyroglobulin, and that the pathological process involved was a progressive destruction of the thyroid due to interaction of the autoantibody in the patient's circulation with thyroglobulin in the gland. They suggested that the precipitin reaction of serum with extract of human thyroid tissue might be a more specific test for Hashimoto's disease than were serum-flocculation tests.

Two recent papers provide further amplification of the subject. In their latest contribution, Witebsky and his colleagues[2] discuss the results of their animal experiments in relation to chronic thyroiditis in man. They found twelve patients with this condition in whom they were able to demonstrate circulating autoantibodies specific against extracts of human thyroid gland, using the tanned-cell hæmagglutination test. Some of their patients had normal or only slightly raised gamma-globulin levels, and only a small proportion of their sera gave a positive response to the precipitin test. They suggest that autoimmunization may occur through a continuous leakage of thyroglobulin into the circulation, which does not happen in normal individuals. This suggestion is supported by the detection of an abnormal iodinated protein in the serum of patients with Hashimoto's disease, recently announced by C. A. Owen and W. M. McConahey.[3] They propose criteria which should be fulfilled before proof of the role of an autoantibody in the pathogenesis of a disease can be admitted, and claim that in their experiments these criteria have been fulfilled. They are chary about committing themselves on the classification of chronic thyroiditis, and conclude that "some types of chronic thyroiditis in man" may be due to autoimmunization against constituents of the patient's own thyroid gland.

Finally, R. B. Goudie and others[4] have used a precipitin test, with thyroid extract as antigen, to study a big series of patients with and without various types of thyroid disease. In 12 out of 16 patients with treated Hashimoto's disease and eight out of 16 untreated patients the result of the precipitin test was positive. The sera from four out of 26 patients with primary myxœdema also gave a positive response, suggesting that in some at least of these cases the same fundamental pathology is involved. Serum from 133 patients without thyroid disease, 17 with simple non-toxic goitre, and four with malignant disease of the thyroid, gave negative results in every case. Positive results from precipitin tests in three out of 120 specimens of serum tested from patients with thyrotoxicosis, combined with the demonstration of complement-fixing antibody to thyroid extract in a majority of thyrotoxic patients, are adduced to support the suggestion that thyrotoxicosis is the primary condition. The theory is put forward that in thyrotoxic patients there is a leakage of antigenic material (probably thyroglobulin) into the circulation; in the majority the antibody response is weak and does not influence the course of the disease; but in a small minority strong autoantibodies are produced, which attack the thyroid cells, eventually causing the changes in gland structure found in chronic thyroiditis. There is some clinical support for this point of view, which may account for at least a proportion of cases of this disease. Thus while it is clear that there is still much that is obscure, and there are some obvious discrepancies between the results of different workers, recent research has thrown much new light on what has for long been a very obscure condition.

A footnote to this discussion is provided by a recent letter from T. Levitt[1] pleading for an international conference to clarify the nomenclature of thyroid disease and to decide on the criteria by which it may be recognized.

[1] *Lancet*, 1956, 2: 820 (October 20).
[2] *J.A.M.A.*, 1957, 164: 1439 (July 27).
[3] *J. Clin. Endocrinol.*, 1956, 16: 1570 (December).
[4] *Lancet*, 1957, 2: 976 (November 16).

THE MENTAL DEFECTIVE IN THE COMMUNITY.

An important issue has been brought into prominence in a recent book by L. T. Hilliard and B. H. Kirman,[2] who with four contributors review progress in the attempts to find a place for the mental defective in the community as against justification for his segregation. It is pointed out that the cursory diagnosis of congenital idiocy is gradually being replaced by more painstaking investigations into the complexity of factors which may be responsible for arrested development of brain and mind. Lower grades of mental deficiency generally are more environmental in origin than higher grades and borderline defect, and the children of dull and backward parents are not invariably defective. Familial incidence appears in neurofibromatosis and tuberous sclerosis, and also in certain metabolic disorders. The authors have noted in their series more cases ascribed to rubella than to syphilis, and consider that irradiation and some of the newer drugs administered to pregnant women are factors to be taken into account. While they discourage the attitude of regarding defectives as pathological curiosities, they have provided good, well-informed chapters on pathological aspects.

In their more positive approach to the ascertainment and disposal of defectives, which provides the main interest of this book, Hilliard and Kerman and their psychologist assistants utter a warning against subservience to intelligence quotient ratings. On the question of how the individual gets on in his particular cultural setting, they see much promise in improvement in social and economic conditions. The distinction between the subcultural and the subnormal is often hard to make, and assessment is often complicated by physical and temperamental handicaps. With the exception of the comparatively few cases due to infection and metabolic disorders, medical treatment has little place; it is a matter for psychologists, educationalists and sociologists. Since illiteracy becomes more and more a handicap in the modern world, time spent in remedying this is well worth while. Further, the defective who is to be placed in industry should be trained in the actual procedures (usually some form of repetition work) and on the types of machines which he will use in the outside world, rather than, as so often happens, in handicrafts which bear no relation to extramural occupations. Under conditions of full employment it has become somewhat easier to find places for defectives, including those out "on licence" from institutions, and a social psychiatry research unit has found that as a class defectives do not tend to present any considerable social problem. Marriage has been encouraged in many instances with success. Critics of this more liberal approach may cast doubt on the diagnosis in many cases in which the subjects have been helped to adjust themselves successfully to life in the community after they have been committed to mental deficiency institutions; but the policy of getting defectives out of institutions rather than of getting them in is worth earnest and sympathetic consideration.

Special problems are reported in this book in some 50 case histories, and the 90 illustrations have been well reproduced from photographs of high quality. There is a good list of references at the end of each chapter. This work, which introduces an enlightened outlook on mental deficiency, should be required reading for the diploma in psychiatric medicine, and demands the attention of ancillary workers in this field.

[1] *Lancet*, 1957, 2 (November 23).
[2] "Mental Deficiency", by L. T. Hilliard, M.A., M.B., D.P.M., and Brian H. Kirman, M.D., D.P.M.; 1957. London: J. and A. Churchill, Limited. 9¼" × 6", pp. 536, with 90 illustrations. Price: 60s. (English).

Abstracts from Medical Literature.

SURGERY.

Acute Volvulus of the Sigmoid Colon.

D. B. HINSHAW AND R. CARTER (*Ann. Surg.*, July, 1957), having studied 55 cases of acute volvulus of the sigmoid colon, classify them into two main clinical types. There is the acute fulminating type characterized by its tendency to occur in younger patients, with sudden onset and rapid course, diffuse abdominal pain and tenderness, and early development of gangrene, and by its frequent simulation of a perforated viscus or other abdominal catastrophe. The other is the subacute progressive type, much more common, which usually occurs in older patients with a more gradual onset and runs a more benign course with slower development of non-viability of the bowel. An acute volvulus of the sigmoid must be regarded as a surgical disease requiring early surgical intervention. The ultimate treatment must be resection of the redundant sigmoid loop. Decompression by means of a rectal tube without operation should be reserved for the occasional patient with the subacute progressive type and no obvious clinical signs of non-viability, whose general condition prohibits laparotomy. At operation all patients with any evidence of gangrenous bowel must be treated by immediate sigmoidal resection or by exteriorization. If the sigmoid is definitely viable, the surgeon may choose between obstructive resection, simple operative detorsion and in occasional cases primary resection and anastomosis. The authors consider that the mortality in acute volvulus of the sigmoid closely parallels the incidence of gangrene of the bowel, and the only factor which can be expected to lower this death rate materially is early operative intervention.

Primary Carcinoma of the Appendix.

J. RABINOVITCH, P. RABINOVITCH, P. ROSENBLATT AND H. ZISK (*Arch. Surg.*, July, 1957) report four cases of primary carcinoma of the appendix discovered during laparotomy for some other disease. They state that such an incidental finding during laparotomy for another disease is a very rare occurrence. They point out that intraluminal carcinomata only will produce symptoms—namely, obstruction and secondary acute inflammation of the appendix. All other carcinomata of the appendix are non-productive of symptoms and can therefore not be accurately diagnosed before operation. The authors state that there is general agreement that metastases in cases of carcinoma of the appendix are late, and that these tumours infiltrate less extensively than do colonic carcinomata. However, a review of the literature also shows poor results with local management of even the apparently less malignant lesions, and they believe that a more radical procedure, such as right hemicolectomy, is the operation of choice. The prognosis for carcinoma of the appendix has never been well established, as few long-term reports are available. In their present series, three patients were alive and well one, five and eight years respectively after appendicectomy and right hemicolectomy. In the remaining case an appendicectomy alone was performed and the patient was alive and well 12 years later.

Surgical Repair of Innominate and Carotid Arteries.

M. E. DE BAKEY AND E. S. CRAWFORD (*Surg., Gynec. & Obst.*, August, 1957) discuss the problems of the surgical treatment of lesions such as aneurysm, tumour, arteriovenous fistula and arteriosclerotic occlusion involving the innominate and carotid arteries. A case is described to illustrate the principles of exposure of these vessels and maintenance of the cerebral circulation during and after operation. Ischæmic damage to the brain is common following arrest of circulation through these vessels, the incidence ranging between 25% and 70%. There is no correlation between the duration of carotid occlusion and the occurrence of neurological disturbance, and tests for the adequacy of the collateral circulation are unreliable. For protection of the brain during the excision and graft replacement of an arteriosclerotic aneurysm of the common carotid and innominate arteries in a 64-year-old woman the authors have used a temporary shunt consisting of a segment of tygon tubing with tooled lucite cannulæ at each end. Longitudinal incisions were made into excluded segments of the arteries above and below the aneurysm and the cannulæ inserted. Removal of the aneurysm and its replacement with a reconstituted, lyophilized, iliac-bifurcation homograft anastomosed to the innominate, subclavian and common carotid arteries required 45 minutes, but by the use of the shunt the cerebral circulation was maintained during this time. The by-pass method is considered superior to that of hypothermia, which is not always effective and which superimposes certain technical difficulties and complicating factors of its own.

Neoplastic Disease of the Spinal Extradural Space.

J. MULLAN AND J. P. EVANS (*Arch. Surg.*, June, 1957) discuss 50 patients with spinal extradural tumours treated by laminectomy and post-operative radiotherapy, six having two operations. There was a wide variety of tumours in this series, 14 being local tumours arising primarily in the spinal extradural space, in the bone or spreading into the extradural space through the intervertebral foramina from the chest. Most of these tumours were *hæmangiomata*. Of the remainder, 15 were reticular tumours, including Hodgkin's disease, myeloma, lymphosarcoma and reticulin-cell sarcoma. Twenty-one tumours were metastatic from the breast, kidney, prostate, lungs and other organs. They attained good results in 32% of patients, 26% were moderately improved, in 14% they considered the result to be worth while, and 28% were "failures". The causes of failure were the high degree of malignancy, the degree of cord damage before treatment, and "errors of judgement and of technique". The best results were obtained in the simpler radiosensitive tumours; the next most favourable were the reticular tumours, whilst the least favourable were the metastatic neoplasms. They consider that all cases of suspected spinal extradural tumour should be investigated urgently by myelography. They think that in cases of unknown histology radiotherapy may be given under close neurological observation where myelographic block is incomplete. If the pathology is known and the tumour is radiosensitive, radiotherapy is given, provided that pressure on the cord is minimal. In all cases when compression is present and the tumour is insensitive to X rays, or when the diagnosis is unknown, or even in radiosensitive tumours where there are marked neurological signs, urgent decompression and post-operative irradiation are indicated. In the presence of spinal cord involvement the need for operation is urgent, and time must not be wasted in prolonged investigation of a suspected primary lesion. In the presence of a complete paraplegia, operation should still be performed, as they had one good result after two months of paraplegia. In no instance was a satisfactory result achieved by a second operation. They consider that if all patients had been referred to hospital before paraplegia was established the percentage of failures would have been 18 instead of 28. They also think that if, in addition, all those referred with evidence of extradural tumour, but without paraplegia, had been operated on immediately upon admission, that figure would have been no more than 10%, which they think is the highest possible figure under present-day conditions.

Gall-Bladder Perforation.

J. R. MASSIE *et alii* (*Ann. Surg.*, June, 1957) review 1253 consecutive gall-bladder operations over a five-year period. Of these 328 were acute or subacute and 925 were chronic. There was a total of 18 perforations. Of these 18 cases six were free perforations into the peritoneal cavity, seven were localized perforations with abscesses about the gall-bladder and five had chronic cholecysto-enteric perforations. In this series there were two deaths, occurring in the last two types. In this series there was one of free perforation with massive intraperitoneal hæmorrhage which the authors claim is only the thirteenth reported in the literature.

Pancreatico-jejunostomy for Chronic Pancreatitis.

M. K. DUVAL, JUNIOR (*Surgery*, June, 1957) discusses 25 patients who had pancreatic duct obstruction with chronic pancreatitis. These patients were subjected to pancreatic duct exploration and decompression by pancreatico-jejunostomy. The characteristics of the disease and operative findings are discussed and details given of the technique of this operation. Among the 25 patients followed for a period up to three years, 20 had remained free of abdominal pain.

All patients gained weight and felt improved, irrespective of elimination of abdominal pain. Four of their patients addicted to drugs were cured of their addiction. The author considers that in selected patients this form of therapy may be of considerable assistance in the management of chronic pancreatitis.

Spontaneous Perforation of the Interventricular Septum.

D. A. COOLEY *et alii* (*Surgery*, June, 1957) point out that spontaneous perforation of the interventricular septum is usually a fatal complication of acute myocardial infarction. Medical treatment is ineffective, and prolongs life only briefly. Death in almost 50% of cases occurs more than one week after perforation, thus providing an interval for diagnosis by cardiac catheterization and surgical intervention. The authors report the case of a 49-year-old female in whom closure of an acquired septal perforation of 11 weeks' duration, resulting from myocardial infarction, was accomplished utilizing a temporary cardiac by-pass. The diagnosis before operation was confirmed by cardiac catheterization. Although the patient died some 45 days later from technical causes, it is suggested that this experience shows that direct surgical correction of this and other complications of acute myocardial infarction may be feasible.

Arterial Grafts and Thrombosis.

W. S. EDWARDS, A. RICH AND E. PETER (*Surg., Gynec. & Obst., August, 1957*) state that arterial grafts acquire a lining which is not true intima of endothelial origin but a modified fibrous tissue, and describe experiments to determine how efficient this new "intima" may be in preventing blood clotting in comparison with normal arterial endothelium. In control animals a three-centimetre segment of aorta was excluded by clamps, the distal clamp being applied first to trap blood in this segment. After the clamps had been in place for one and a half or two hours the segment of vessel was rapidly removed and examined for evidence of clotting. No clot formed in 90% of the cases where the aortic segment was clamped for 90 minutes. Extending the clamping period beyond 90 minutes led to a higher incidence of thrombosis in normal vessels. For this reason one and a half hours was chosen as the test occlusion period for the grafted vessels. Observations were made on segments of crimped nylon grafts in 10 dogs at intervals of four to 18 months after grafting, and on aortic homografts in five dogs at intervals of five to seven months after grafting. The incidence of thrombosis in the homografts and nylon grafts was approximately the same, thrombosis being found in three nylon grafts and in two of the homografts. The clots in most instances were attached to an "unhealed" area of granulation tissue which had not become organized to a smooth pearly surface. The authors conclude from this study that the new lining of grafts, when completely organized, compares favourably with normal intima in preventing clotting of a stationary column of blood, and that stagnation of blood in a graft of any kind prior to complete healing of the lining will lead to thrombosis. It is suggested that, in patients with femoral grafts, sitting with legs crossed or sleeping in an awkward position, may lead to slowing of the blood flow and is potentially dangerous until such time as the fibrous lining of the graft has organized into an unwettable surface.

Plaster of Paris to Fill Defects in Bone.

L. F. PELTIER *et alii* (*Ann. Surg.*, July, 1957), experimenting on dogs, found that plaster of paris is absorbed from areas of implantation in bone and is well tolerated by the tissue. Associated with this absorption bony regeneration from endosteal and periosteal cells occurs. The plaster of paris does not prejudice wound healing or provoke a foreign body reaction. The authors do not consider that the plaster of paris itself stimulates osteogenesis. Its chief effect is a mechanical one of preventing the collapse of the periosteal tube and favouring regeneration in this way. Periosteal resections in which plaster of paris columns were inserted regenerated more frequently than was the case in subperiosteal resections alone. The authors think that this material may find a greater application in clinical surgery when its behaviour becomes more widely appreciated.

Electrical Ventricular Defibrillation.

A. B. KOBTZ AND H. SWAN (*Arch. Surg.*, June, 1957) conducted a series of experiments on mongrel dogs in which they performed transsternal thoracotomy and right ventriculotomy during hypothermic anæsthesia. If ventricular fibrillation occurred during the experiment, defibrillation was attempted by injecting epinephrine 1 : 10,000 solution into the right side of the heart, intermittent manual cardiac compression was performed for one minute, and electrical defibrillation was attempted by applying single or coupled shocks of 170 or 220 volts for 0·13 or 0·20 second with bare electrodes (two inches in diameter) placed at the right auricle and cardiac apex. They found that there was a high late mortality in those dogs in which "successful" defibrillation was accomplished. It is considered that this was a result of the method of defibrillation rather than of the arrhythmia itself. They present a practical technique of ventricular defibrillation which emphasizes the importance of avoiding electrical burns and which imposes a low intrinsic mortality. The authors point out that although ventricular fibrillation may be relatively innocuous when properly treated, they do not subscribe to the elective production of this arrhythmia during open cardiotomy. They believe that a regular sinus rhythm, with or without periods of elective cardiac asystole, is desirable during intracardiac and extracardiac procedures. They state that should ventricular fibrillation supervene, electrical defibrillation can be readily executed, but must be performed without the production of myocardial or epicardial burns which may preclude adequate cardiac function in the period following defibrillation. The prevention of such burns is achieved by interposing a pad soaked in saline between the heart and the defibrillator electrodes. This is not a new technique, but the authors claim that its relation to post-operative mortality has not been previously appreciated. It is suggested that the manufacturers of electrical defibrillating devices should advise their clients regarding the importance of this facet of the successful application of their product.

A Clinical Study of Cancer of the Gingiva.

S. A. WILKINS AND W. R. VOGLER (*Surg., Gynec. & Obst.*, August, 1957) have studied 81 gingival growths, comprising 79 squamous cell carcinomata, one adenocarcinoma and one chrondrosarcoma. They suggest that the use of tobacco is an etiological factor and that the unusually high proportion of females affected (54%) is related to the habit of snuff-dipping still prevalent among certain women of the South. The part of artificial dentures in the development of cancer could not be established from the available data. Forty *per centum* of the patients had leukoplakia on some portion of the buccal mucosa in addition to the cancer. Fourteen of the patients had multiple primaries. Treatment consisted of irradiation or surgery (with a preference for the more conservative procedure where possible), or a combination of the two. Five-year figures are given for a group of 30 patients. Of these, nine, or 31%, survived five or more years without recurrence. In this group nine patients had metastatic nodes in the neck when first seen, and of these two were cured, one by surgery and one by irradiation followed by surgery. In a group of 32 patients followed for two to five years, 12, or 40%, are considered to have two-year cures. In an analysis of the failures local recurrence is seen as the main problem. Almost all the failures were recognized within the first two years after treatment. Surgery and irradiation are equally effective in the initial treatment of localized lesions, and the selection of one of these procedures over the other was made on the basis of certain factors other than the anticipated chance of cure. Surgery is to be preferred for patients with extensive lesions or with metastases to regional nodes.

Paradoxical Hypertension Following Resection of Coarctation of Aorta.

W. C. SEALY *et alii* (*Surgery, July, 1957*) point out that after a repair of a coarctation of the aorta a significant elevation in the blood pressure may develop and regress in the first 36 hours. This is of no clinical significance. A delayed and more ominous type of hypertension, principally diastolic, may occur on the second post-operative day. In some patients this is associated with abdominal pain. Occasionally this pain may continue, and then small bowel necrosis occurs. In fatal instances arterial necrosis has been found localized to vessels originating from below the coarctation site. In the survivors the increased pressures and symptoms have subsided without sequelæ in 14 to 21 days.

British Medical Association.

NEW SOUTH WALES BRANCH: SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held in the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, on October 24, 1957, DR. G. L. HOWE, the President, in the chair.

Painful Shoulder.

DR. NAOMI WING read a paper on the subject of painful shoulder. This was substantially the same as the paper read in Melbourne to the annual meeting of the Section of Physical Medicine and Rehabilitation (British Medical Association) and published in the issue of December 14, 1957.

DR. C. J. R. CONACHER read a paper on the orthopaedic aspects of painful shoulder. He said that to his mind the remarkable thing about the shoulder was that it ever worked at all and that pain was ever absent. From all points of view it was a bad risk. There were not one but four joints to go wrong, and for good function they must all work synchronously. Although it was extraordinarily mobile, with 180° or more of movement in several directions, and subject to injury in many ways, the nerves and vessels which it cradled were seldom harmed. Far back in evolution the shoulder had attached a fin to a fish and had had the stresses and strains of a paddle or a hinge. Later it had borne weight, but now it was a prehensile joint with a tendency to separation of joint surfaces and with great strain thrown on the soft tissues which held those joint surfaces together. Apart from its own mechanical absurdities, the area was supplied by nerve roots passing through an extremely mobile and vulnerable part of the spinal column. It was the site of pain referred from structures which migrated caudally from the neck in the embryo, especially the diaphragm and the heart. Furthermore, it was a gauge of general health and reacted to anaemia, debility, overwork and constitutional disease.

The truth, of course, was that, like a car, the shoulder might look fine and feel fine and yet might be worn out inside. After the age of 30 years most shoulders were to some extent worn out inside. The soft tissues took the strain and suffered for it, but mostly they suffered in silence. Ligaments, tendons, cartilages and synovia in and about the gleno-humeral joint degenerated. The ligaments and tendons became shredded, frayed, torn and fibrosed. For the most part it was only when there was secondary inflammation that pain appeared.

The "painful arc" was widely regarded as diagnostic of something called "supraspinatus tendinitis", and truly enough it was often caused by inflammation of the rotator cuff in the supraspinatus area, but that inflammation was secondary and not primary. The inflammation might be secondary to degeneration in a rotator cuff, calcareous tendinitis, complete or incomplete tears of the rotator cuff or subacromial bursitis. A painful arc might also appear in affections of the acromio-clavicular joint, lesions of the greater tuberosity or bicipital tenosynovitis. In bicipital tenosynovitis there was no painful arc, as the arm was abducted, but it might be present as the arm was let down from the fully abducted position.

Bicipital tenosynovitis was quite common, although frequently not recognized. Clinically there was accurately localized tenderness along the bicipital groove, and there tended to be more spasm than in other forms of shoulder pain, except, of course, hyperacute calcareous degeneration. The onset of symptoms might be sudden or gradual, and might or might not follow injury; the injury might be of almost any sort, direct or indirect, single or repeated. Bicipital tenosynovitis might be associated with dislocation of the tendon. With a dislocating tendon a snap could be felt as the arm was elevated and rotated externally while the patient was holding a five-pound weight.

Two diagnostic tests were described, but neither was of great value. Yergasson's sign was supposed to be "positive" if there was pain on active contraction and relaxation of the biceps when the shoulder was held by the side. However, under those circumstances, the long tendon of the biceps did not move in the bicipital groove; the humerus moved on the tendon during movements of the shoulder joint; otherwise, there was obviously no movement of the tendon in the groove. There was also Lippmann's sign, in which the patient actively tightened the biceps with the elbow flexed to 90° while the examining surgeon seized the tendon just below the bicipital groove, pulled it to one side and let it go; if the sign was "positive", there was pain at the end of the manœuvre.

On the subject of rotator cuff tears, Dr. Conacher said that the rotator cuff was such a strong structure that a diagnosis of a tear was often not made because the injury was thought to be insufficient. However, in the vast majority of cases the tendon which tore was already degenerated and quite a minor injury might disrupt it. Proven tears had been recorded without any injury at all. That primary degeneration had a bearing on treatment too. When one saw what was clinically a complete tear, it was very tempting to go in and sew it up nicely. But in those cases the torn edges were fibrotic and avascular, and even if anatomical reposition was possible (which it very seldom was), there was no hope of its healing by first intention. The right thing to do was to wait two or three weeks, using a sling and progressive active exercises. If by then there was no improvement whatever and the diagnosis was undoubted, operative repair might be considered. Otherwise, one should wait until improvement ceased and then reassess the problem. If an abduction splint was used in conservative treatment, not only did separated ends fail to appose, but the retracted tendon stump was actually compressed between the acromion and the humerus; that further hindered a blood supply which was already poor. If operation was decided upon the aim was: (i) to produce apposition of healthy tissues without tension, (ii) to provide a smooth surface under the acromion (or alternatively to perform an acromionectomy), and (iii) to divide the coraco-acromial ligament. Repair might be possible through a deltoid-splitting incision, but partial (or even complete) removal of the acromion might be necessary.

Dr. Conacher then discussed treatment. He said that all acute disorders, of course, needed rest, and a sling was usually the best way of providing that; abdution splints were usually less effective. Heat or cold might help; analgesics made life tolerable. Of vital importance was progressive active exercise. Practically any painful shoulder immobilized without exercise could lead to a "frozen shoulder". When physiotherapy was ordered, it should be carried out intelligently, and details should be specified. Sending problem patients for heat and massage and "lamps" was deplorable. Specific treatments might be indicated as in gout, for which colchicine or "Butazolidin" might be very helpful.

The general health should be looked into; anaemia, debility or overwork might precipitate or perpetuate symptoms due to intrinsic causes.

Cortisone could be very helpful. The tissues of the body had only one way of reacting to insult—by inflammation—whether that insult was a bacterial infection or an injury. Cortisone reduced the inflammatory reaction, whatever the cause might be; if the inflammation was bacterial, such hindrance could be catastrophic; however, if it was the result of trauma, and if the inflammation was serving no useful purpose, cortisone could be very useful. Because of its prehensile function and liability to injury and degeneration, the shoulder was the site of a lot of useless aseptic inflammation, which could be reduced by cortisone. However, it affected only the inflammation and not the cause of the inflammation. If the cause of the inflammation was a transient incident like trauma, all was well and good; but if the basic cause persisted, as in degenerative lesions of the shoulder, the initial symptoms might well recur when the action of the cortisone ceased. Hydrocortisone was useful in the shoulder, as the affected tissues were often easily accessible. It was particularly useful for tears, for calcareous tendinitis, for bicipital tenosynovitis and for coraco-clavicular strain and arthritis. In Dr. Conacher's experience hydrocortisone in frozen shoulders administered according to a technique similar to that described by Dr. Wing was useless. In using hydrocortisone anywhere the lesion must be very accurately pin-pointed and the injection made precisely into the affected tissue. Great care must be taken with asepsis, as there was a very real danger of local infection. If an organism sneaked in with the needles, the inflammatory reaction of the tissue was inhibited. Sometimes the injection material had to be pumped into dense tissues, and considerable force might be necessary to push the plunger home; Dr. Conacher found a lumbar puncture syringe useful. He had not found the later modifications to be any better than the original drug.

For some lucky doctors orally administered cortisone in the active stage of "frozen shoulder" suppressed the condition and enabled exercises and so forth to keep the shoulder in good condition pending recovery from the active state; but orally administered cortisone was not much use

for Dr. Conacher's patients because: (i) few could afford it—it cost £4 or more a week; (ii) frozen shoulder commonly affected people with cardio-vascular, pulmonary, metabolic or gastro-intestinal disorders, which contra-indicated cortisone; (iii) even with the new forms of cortisone he was reluctant to use the dosage often prescribed (or equivalent doses of the new preparations)—200 milligrammes of old cortisone until relief of symptoms and very gradual reduction; small doses had been ineffective in his experience.

Orally administered cortisone was also said to be very effective for calcareous degeneration in all but the chronic stages and sometimes for bicipital tenosynovitis, but again Dr. Conacher's experience had been disappointing.

Manipulation with the patient under "Pentothal" anæsthesia was some help in the late stages of frozen shoulder, but some people said that the improvement was subjective rather than objective. It should be performed with cortisone cover where possible. There was a real risk of fracturing the neck of the humerus.

In the treatment of calcareous degeneration the principle of rest in the acute stages with sufficient movement to prevent stiffness applied there as everywhere else. In the hyperacute stage all treatments must be assessed against the knowledge that the real agony would pass in a few days, and that opiates could help the patient over that period. Available treatments were, in decreasing order of effectiveness, the following: (i) Surgical removal of the lesion. That gave immediate, complete and final cure. Dr. Conacher said that he thought he would choose that course himself; but when it came to the point and the choice was left to the patient, he usually declined operation. (ii) Irrigation with two needles, aspiration and acupuncture all in one. That was frequently effective, but it was distressing to the patient, and some people did it only with the patient under a general anæsthetic. Surely, however, if a general anæsthetic was necessary, it was better to deal with the condition surgically and finally. (iii) Hydrocortisone injection. The aim was to reduce the inflammation. Occasionally hydrocortisone made it worse for a day or two. (iv) A sling, ice-bags and opiates.

In the less acute stages the medical situation was similar, but few people would elect to have surgical operation. Hydrocortisone was very useful in that case and must, of course, be combined with active exercises. Radiotherapy had a good reputation, and Dr. Conacher said that he would be interested in Dr. Corlette's views on that. It was wise when an acute attack had settled to have radiotherapy to lessen the chances of recurrences.

Turning to the question of operation, Dr. Conacher said that surgery was the last weapon in the arsenal, and it was one which should be used reluctantly. But first there was one outstanding contraindication—long-standing stiffness.

Without question the removal of calcareous deposits in the presence of hyperacute symptoms was very effective; the relief of symptoms was immediate and complete, and there were no late pains or recurrences. The patient was propped up in a semi-sitting position and with the arm free to move. The approach was by a short deltoid-splitting incision over the point of maximal tenderness; the arm could then be rotated and abducted until the lesion was found; that was usually not difficult. The fibres of the deltoid could safely be split for a distance of one and a half inches below the acromion process without injuring its nerve supply. The coraco-acromial ligament should also be divided; that reduced post-operative pain and left no late disability.

In patients who had persistent "painful arc" symptoms from any cause associated with the acromion, excision of the acromion process could be effective. Most surgeons had had or had seen bad results of acromionectomy, but it was quite wrong to assume that those were the only results. When an appendix was taken out, the details of the surgeon's operative technique and the details of the after-care had little effect on the late result, granted the patient's survival. That was so with most general surgical procedures, but it certainly did not hold for orthopædic surgery in general and for acromionectomy in particular. There the minor details of the technique and after-care could make the difference between dramatic success and failure. The most important point in the operation was to attach the deltoid strongly to the trapezius by tension sutures. The deep part of the centre of the deltoid origin was a tendon about the thickness of a match stick or a bit more; it was essential to stitch through that. In the after-care early restoration of function was vital; one way was to nurse the arm on an abduction splint, but to commence shoulder elevation exercises in ten days, the splint being discarded when abduction was strong.

In patients with bicipital tenosynovitis, with or without dislocation of the tendon, the symptoms might be very persistent. The condition could be relieved by detaching the tendon from its origin and fixing it elsewhere, preferably to the floor of the bicipital groove.

In conclusion, Dr. Conacher said that he had intended to carry two messages. The first was that hydrocortisone was very useful indeed, but accurate diagnosis and very careful injection technique were vital to the chances of success. The second was that operations, particularly for removal of calcareous deposits with hyperacute symptoms and acromionectomy, could be very successful.

DR. P. M. C. CORLETTE, in opening the discussion, said that as a radiotherapist he had nearly always seen patients who had been to at least one doctor, if not many. Consequently, there was often a ready-made diagnosis, or the patient came with the plea from his doctor: "We have tried everything. Do you think X-ray therapy might help?" With regard to the last question, Dr. Corlette said that one was unfortunately often inveigled into treating some condition against one's better judgement, as the result of the desperation of the patient and of his doctor. Occasionally, of course, a surprising result was obtained, and the prime rule on such occasions was never to appear surprised, but to appear as if one had really expected what had happened.

Dr. Corlette went on to say that in the treatment of a "painful shoulder" diagnosis was all-important. That was particularly so to him; if he was to treat a shoulder by radiotherapy, the diagnosis should be clear cut, as he felt that only certain conditions would be benefited, and such a mode of therapy as irradiation should not be used unless there was a good chance of cure or relief of pain. In patients coming to his care with shoulder pain, the broad divisions were those of disease, benign and malignant, and of situation, articular and periarticular, or distant and referred.

Dr. Corlette then referred briefly to five malignant conditions commonly met with in the upper end of the humerus and scapula giving rise to pain, and indicated their management. The first of these, osteogenic sarcoma, was primarily a surgical condition, and only secondarily of radiotherapeutic interest. The second, Ewing's tumour, of which the upper end of the humerus was an occasional site, was a disputable pathological entity, and many cases were now considered to be either solitary reticulosarcomas or secondary neuroblastomas. Biopsy should give the diagnosis, though the matter was often one of pathological dispute. As a therapist, he considered the distinction was important, as the tumours which were really solitary reticulosarcomas were curable by means of irradiation. Dr. Corlette thought that they were the cases that made up the real cures in the literature of Ewing's tumour. The third was myeloma, presenting as a solitary cyst, treated by irradiation, but a precursor of things to come, eventually becoming generalized, as multiple myeloma. For the fourth condition, metastatic carcinoma from the breast, prostate and other organs, the bones around the shoulder were a common site; the pain was immediately relieved by radiotherapy. The fifth condition, sarcoma, was not usually relieved by irradiation, but the special circumstance of pain due to sarcoma supervening on Paget's disease should be mentioned; that pain was usually relieved by X-ray therapy, as was the pain associated with Paget's disease itself.

Turning to the question of simple tumours, Dr. Corlette said that he would mention two only. Solitary bone cyst of the humerus was generally a surgical problem, but it was occasionally treated by irradiation owing to the size of the tumour and the likelihood of damage to the joint from surgical intervention. Osteoclastoma or giant-cell tumour gave uniformly good results when managed by radiotherapy alone, though it was often treated by surgery.

With regard to pain in relation to the site of the lesion, Dr. Corlette referred to the pain associated with periarticular structures and that due to neurogenic causes. The common condition that he saw was one of calcified deposits in the rotator cuff of the shoulder, calcareous tendonitis or degeneration, particularly in relation to the supraspinatus. Again, diagnosis was important; if there was a tear of such a cuff, the pathological condition was more severe, and X-ray therapy was useless and even harmful. Dr. Corlette said that he found it hard to say whether X-ray therapy for supraspinatus tendonitis should be one of the main and early forms of treatment, or whether other methods should be tried first. Certainly, in the early cases, the results of

X-ray therapy were most dramatic; but so could be the results of hydrocortisone injections. Irradiation was certainly painless, and it involved no handling or movement of the limb. It was known, of course, that the acute disease was self-limiting, and would subside spontaneously, but that was hardly of comfort to the sufferer. Relief was certainly prompt following X-ray therapy, and recently Stoll, of Melbourne, had published results in 21 cases; in most of those the patients had previously had treatment with diathermy, "Butazolidin" and "Novocain", and had suffered from pain for some three months. Of the 21 patients, 19 obtained relief in a week, and that was the common experience of the radiotherapist. Dr. Corlette said that the mode of action of such treatment was uncertain. The effect of X rays on tissue was the destruction of leucocytes, and of rapidly growing cells, increased permeability of cell membranes and increase of blood flow. The increase of blood flow might be the cause of the occasional exacerbation of symptoms seen after X-ray therapy. Hydrocortisone sometimes had the same effect, and Dr. Corlette said that he understood that its effect in the tissue was to decrease the number of granulocytes and the total cell count; thus there was some similarity of action to that of X-ray therapy. In the presence of calcification the active hyperæmia possibly speeded up the solution and absorption of calcium deposit. Other causes of pain in the shoulder were arthritis, either post-traumatic or degenerative. Occasionally in such cases X-ray therapy produced relief, but all other methods should be tried first.

Of neurogenic causes, those due to distant disease, one occasional cause of shoulder pain was cervical radiculitis. In such cases, when the pain was the result of a degenerative condition of the cervical part of the spine and osteophyte formation around the cervical foramina, and other methods of treatment had failed, a gratifying response was often obtained from a short low-dosage course of X-ray therapy to the cervical part of the spine.

Dr. Corlette said that a question might be asked about the dangers of using irradiation in the treatment of benign conditions. The dosage used for the conditions under discussion was usually of the order of several hundred Röntgens in a period of eight days. The filtration was light, so that penetration was not deep, and the portal of entry was kept quite small. He thought that the question of genetic effect did not have to be considered. Any general effect was most improbable at such a dose level. Such cases of leuchæmia as had been reported after X-ray therapy, and had showed a definite statistical relationship to it, had all occurred when the dosage had approximated 2000*r* and had been given to large and multiple fields, with consequent irradiation of a large amount of bone marrow.

DR. W. A. HUGH-SMITH said that he disagreed slightly with Dr. Wing on the question of the manipulation of the frozen shoulder, by which he understood the fixed shoulder was meant. Sometimes such manipulation was indicated, but its use had fallen into disrepute, because some people had been in too much of a hurry to carry it out. It might be necessary to wait three or six months before the joint was ready for such treatment. He had no faith in physiotherapy for the frozen shoulder. He believed that it was more important to try to get the patient back to some type of work, except when the condition was associated with other disabilities such as an affection of the heart. He wondered whether the condition of bicipital teno-synovitis was common. He agreed with the criticism that had been levelled at the abduction splint; it had been invented by the devil and had no place in treatment, except for certain fractures in young people. Expressing interest in the helpful results obtained with hydrocortisone, Dr. Hugh-Smith said that he could not understand how the injection of the substance into an acutely calcified supraspinatus tendon could relieve pain; surely the injection of anything would increase tension and so pain. He agreed that operative treatment was occasionally necessary for calcification in the early stages, but most patients lost their pain in a few days if one waited. He remarked that great help could be obtained from the radiotherapist in the treatment of capsulitis in the elderly patient.

DR. LINDON WING said that he was interested in the injured shoulder as it occurred in industry. In the past year, he had had to do with 27 men who were off work for more than two weeks with an injured shoulder. From his observation in those cases and from his experience in practice in the country, he commented on three possible forms of treatment. The old form of conservative treatment with heat and physiotherapy eventually cleared up the condition; but it took a long time, with persistent pain, and the patient was off work for a prolonged period. Hydrocortisone given correctly produced relief quickly, and the patient was back to work sooner than with the older forms of treatment. Manipulation did not hasten the response.

Dr. Howe, from the chair, told the story of a patient who had obtained complete recovery some time after receiving a lump sum payment as compensation for a painful shoulder, resulting from injury while at work. He pointed out the importance of being patient, as complete recovery would often occur if one waited long enough.

Dr. Naomi Wing, in reply, said that it was important in referring to physiotherapy not to confuse the old-fashioned massage with a full programme of physical medicine as it was used today. The treatment of patients with such conditions as a painful shoulder was a matter for teamwork and the use of all available resources to restore them to usefulness. The attending doctor should be sufficiently acquainted with modern techniques to be able to give detailed written instructions to the therapists who would carry them out.

Dr. Conacher, in reply to Dr. Hugh-Smith, said that he agreed that the injection of hydrocortisone probably increased tension, but that the fluid excipient soon became dissipated, the active agent being left behind.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

AN AUSTRALIAN MEDICAL WOMAN PIONEER.[1]

[From the *Australasian Medical Gazette*, March, 1890.]

AT the meeting of the Medical Board of Victoria held last month Miss E. Constance Stone was registered as a medical practitioner, being the first Australian lady doctor who has been granted registration in the Australian colonies. This young lady, whose parents reside in St. Kilda (Melbourne), left there some six years ago to follow out a course of medical study. This was necessary at the time as no opportunities were then afford to ladies to prosecute medical studies in our universities. Dr. Constance Stone first graduated at Philadelphia, obtaining the M.D. degree, and after being assistant medical physician at the Women's Hospital, Staten Island, New York, she proceeded to Canada and at Toronto obtained her M.D. and C.M. degree. She next sailed for England and succeeded in obtaining the L.S.A. diploma, after which she was physician's assistant at the New Hospital for Women, London. Her medical studies covered six years. We heartily congratulate Dr. Constance Stone on her being the first lady registered as a medical practitioner in Australia, and wish her the highest success, both pecuniary and social, in her professional career now commencing.

Correspondence.

MATERNAL AND FŒTAL PROGNOSIS IN TOXÆMIA OF PREGNANCY.

SIR: It was flattering to read Dr. Chesterman's remarks in his letter on this subject in your Journal (October 26, 1957), but I am afraid that what he has written does not really explain how severe preeclampsia and eclampsia were both reduced in incidence at The Women's Hospital, Crown Street, suddenly and remarkably, during the years 1948 to 1952.

These were the years when I had the honour of superintending the hospital, and I saw personally (at some stage of the pregnancy, labour or puerperium) the vast majority of the 18,000 booked patients delivered throughout those years. I must say at once that I did not regard the sphygmomanometer as the basic instrument on which we built our success then. There were sphygmomanometers at

[1] From the original in the Mitchell Library, Sydney.

The Women's Hospital long before I began my work there, and these instruments had, of course, been employed intelligently and conscientiously at the hospital by obstetricians of great ability for a very long time. Weighing machines had also been in use at Crown Street for a decade before my day. By 1947, indeed, the hospital could look back upon a vast experience extending over half a century, and upon a succession of attempts to improve its ante-natal care; yet the booked eclampsia rate remained high.

Four years later, as is well known, the rate had been reduced almost to vanishing point. Many people and many factors contributed to this achievement, and behind all our efforts were the indomitable faith and energy of the chairman of the honorary medical staff, the late Dr. Dixon Hughes.

In a paper published in *The Lancet*, I have described the methods used which led (in my opinion) not only to this result, but also to an accompanying profound fall in the prevalence of moderate and severe preeclampsia, and to a gratifying salvage of fœtal life (at the rate of 50 babies *per annum*). It can be assumed that my paper gave a reasonably accurate description of the methods employed from 1948 to 1952, because it was read and approved for publication by Dr. Chesterman and the entire honorary medical staff. Those who read my paper will have observed that scant reference was made to blood pressure records. This was done deliberately, because, as the chief admitting officer of the hospital, I found the blood pressure readings of ante-natal patients to be of limited value. I do not make this statement lightly, but base it on a good deal of evidence. It is based, in fact, on a close personal study of the complete ante-natal blood pressure records of more than 12,000 patients delivered at that time. May I quote the case history of one patient, to demonstrate how dangerous it can be to rely basically on the sphygmomanometer in a campaign against eclampsia?

Antenatal Record (Abridged) of A., aged 23. Primipara.

Date.	Weeks' Gestation.	B.P.	Urine.	Weight.
23.6.48	12/52	120/80	Clear	9 stone 8 pounds
9.9.48	26/52	120/80	Clear	11 stone 9 pounds
25.11.48	34/52	110/80	Clear	11 stone 10 pounds
8.12.48	36/52	105/70	Clear	11 stone 12 pounds
15.12.48	37/52	100/65	Clear	11 stone 12 pounds
22.12.48	38/52	112/80	Clear	11 stone 13 pounds

25.12.48: Early labour. B.P. 110/80. Urine clear.

27.12.48: Early labour. B.P. 130/75. Urine clear.

28.12.48: Urine clear. Eclamptic fit. B.P. 140/110 after fit. Albumin 1/10. Three fits occurred.

This patient's B.P. was 120/80 at 12 weeks and 110/80 three days before the fits occurred. It rose to 130/75 in labour 24 hours before the fit. No albuminuria was present before eclampsia occurred. Here, reliance on the B.P. and urine test gave a false sense of safety until 24 hours before eclampsia occurred.

I have the records of nine other similar disappointing cases, in which the sphygmomanometer failed to give fair warning of the approach of convulsions.

I was present at the Rotunda conference referred to by Dr. Chesterman, and heard Green, of Melbourne, Fitzgibbon and Falkiner and others express their disappointment at the results of classical ante-natal care in the field of toxæmia. Our results in Sydney up to the middle of 1948 were equally disappointing. This called for a new prophylactic regime, which was gradually developed throughout the next two years, and was based on a consideration of three obvious clinical observations.

1. Most severely preeclamptic women in late pregnancy are so obese and œdematous that they bear a striking resemblance of one another, when their disease is in full flower. The resemblance depends on a gross change in habitus. My own observations during these years (and those of Stevenson[1] before me) showed that the alteration in habitus often began at the twentieth week or earlier.

2. An investigation of the foods eaten by preeclamptics (McNaughton,[2] Hamlin[3]) proved that they usually ate excessive amounts of refined high-calorie carbohydrates (especially derived from wheat), which contained a hidden complement of sodium chloride or sodium bicarbonate. This excess of floury carbohydrate raised the sodium intake, increased the total Calories and reduced the proportion of protein and vitamins.

[1] M. J. AUSTRALIA, 1952, 1: 320.

[2] National Health & M. Research Council, 1948, Australian Ref. Series No. 4.

[3] *Lancet*, 1952, 1: 64.

3. It became apparent that classical ante-natal care had failed because it concentrated its vigilance especially on the last 10 weeks of pregnancy. Interest was, until 1948, directed, not upon the prehypertensive phase of preeclampsia, but upon the established entrenched disease. Under the accepted order, no active steps were taken to combat toxæmia until it could be measured against such uncertain measuring rods as the level of the blood pressure or the presence of albumin in the urine. The old care frequently recognized and treated toxæmia only when it was too late to halt its gathered momentum by late pregnancy dietings, late salt depletion, sedation, *Veratrum viride* or venesection.

The New Prophylaxis, 1948 to 1952.

This has been described in my papers published in *The Lancet*[1] and in the *Proceedings of the Royal Society of Medicine*.[2] Its essentials may be referred to under three headings:

1. *First Visit.*—Diet education was begun at the first visit and was made most emphatic in the first half of pregnancy. The patients were not bored and burdened with rigid printed instructions. They were given slogans instead of diet tables. They were told "to lay down the bread knife and to take up the carving knife", and "to avoid excess of wheat and to live on plenty of meat". They were not asked to starve or to be hungry.

2. *First Twenty Weeks.*—Those patients who gained more than three-quarters of a pound per week in these weeks were taught what to eat by the dietitian. If they could not or would not cooperate, they were admitted to the wards for practical diet instruction. The ante-natal beds were trebled in numbers to provide ante-natal accommodation for all who needed it in the series of 18,000 patients.

3. *Twentieth to Thirtieth Weeks.*—At this critical period the patients were studied, not primarily with the sphygmomanometer and the urine test, but with the eye and the weighing machine, for the onset of prehypertensive preeclampsia. (I realize, of course, that, rarely, cases of "dry" preeclampsia occur, in whom there is no œdema and no excessive weight gain.) Prehypertensive preeclampsia, especially in primigravid patients, has three clear signs, usually manifested towards the end of the twentieth to thirtieth week period. They are: (*a*) A rate of weight gain of eight pounds or more in any ten-week period before the thirtieth week. (This degree of weight increase is not necessarily of importance in multiparous patients.) (*b*) Slight tightening of the engagement and wedding rings, and perhaps a minimal œdema of the legs. (*c*) A tell-tale whitening of the infra-orbital skin (white "rings" under the eyes) due to early subcutaneous œdema of the lower eyelids in incipient toxæmia. This is accompanied by a slight rounding of the facial contours, which does not amount to the puffiness of late toxæmia.

Patients showing these signs were admitted to the wards for a high-protein, low-calorie diet in which carbohydrate was reduced, and salt greatly restricted. Such treatment, together with bed rest, usually arrested or slowed down the progress of the disease, so that the hypertensive phase was either not reached, or was delayed until pregnancy was far advanced, or until labour began.

Experience with this sufficiently large series of cases indicated that if the obstetrician will faithfully carry out such a regime throughout the first 30 weeks of a patient's pregnancy, the last 10 weeks will seldom trouble him. And even if these measures fail, as, of course, they sometimes do, the old weapons for the treatment of established preeclampsia are still available and can be employed. Nothing has been lost.

Of course, the new prophylaxis of toxæmia calls for a new look and a new deal in ante-natal care. It demands a change in our conception of what pre-natal education and supervision really mean. It involves a much closer supervision and control of out-patients, the acceptance of what may appear to be slender indications for the admission of patients for indoor care, and a radical redistribution of the beds in obstetric hospitals. The old planning allotted only 10% or 20% of the beds for ante-natal patients; the new deal requires that one-third of the accommodation is reserved for them. For, as Peel[3] points out, "no price is too high to pay for the elimination of eclampsia which still causes a maternal mortality of 5 to 10 per cent.".

If all these things are done, if preeclampsia is searched for and treated in its prehypertensive phase, the maternal

[1] *Proc. Roy. Soc. Med.*, 1953, 46, No. 5.

[2] *Practitioner*, 1957, 179: 371.

and fœtal prognosis in toxæmia will be greatly improved. The striking success reported from Crown Street in 1952, achieved by these measures, stands unshakably as the proof of their efficacy.

Yours, etc.,

R. H. J. HAMLIN.

20 Victoria Avenue,
Rose Park,
South Australia.
November 29, 1957.

RADIATION GENETIC HAZARDS OF A POPULATION.

SIR: Dr. Ilbery's article on this subject (M. J. AUSTRALIA, November 23, 1957) states that "clinicians should be aware of those examinations which contribute most to the genetic load". As this point has received little publicity, I feel your readers might be interested in fuller details. In diagnostic radiology, genetic hazards are almost confined to examinations of young and middle-aged persons in which the gonads are in the direct beam of radiation. This would include X rays of the hips, pelvis, sacrum, coccyx, sacro-iliac joints, and bladder, cystograms, intravenous pyelograms, salpingograms, and barium enemas. Stanford and Vance[1] found that the gonad dose from such examinations is of the order of 1*r*, although there is much variation. In examinations of other parts of the body where the gonads are shielded from direct irradiation, the gonad dose is much lower; for example, in a single chest X ray, it would be of the order of 0·0002*r*, which is about the amount that a person receives in one day from natural sources. X-ray examination of the upper abdomen may also carry a high gonad dose, but some of the higher figures reported may be due to insufficient shielding of the gonads. The commonest examinations with high genetic dose are of the hips and pelvis in males, and intravenous pyelography, lumbo-sacral spine and pelvimetry in females.

Uncooperative infants of one to three years may be a problem, as they may require several people to hold them still. As the child wriggles and screams, safety precautions are liable to be relaxed, so that a skull X ray (with perhaps several repeated films) may result in both patient and parents or nurses being liberally sprayed with X rays.

Genetic hazards do not occur in sterile persons. They are of minor importance in persons unlikely to beget children, such as women over 50 and men over 55. They would be more serious in a healthy young person who might beget many children.

It is usually the clinician's responsibility to balance the potential dangers of the examination against the possible benefits in each individual patient. This is made hard by the uncertainty of the genetic risk of a given dose in man. The risk is certainly small, since genetic ill effects have been very hard to demonstrate in man, even when many offspring have been observed following an atomic bomb explosion (Medical Research Council[2]) or radiotherapy of the ovaries with up to 175*r* (Kaplan[3]). Analogy from experiments on mice (Russell[4]) would indicate that if the gonads receive a dose of 1*r*, then about one in every 1000 offspring will carry a harmful mutation. It is a matter of opinion whether these mouse figures apply to man.

It seems to me (although perhaps I am biased) that diagnostic X rays in the pelvic region will be justified whenever there is a reasonable chance that treatment of a dangerous or potentially crippling disease might be improved as a result, or if it would help in the planning of or the decision for an operation. Most X rays of the pelvic region are in search of potentially serious disease. For example, fractures of the hip and pelvis, urinary tract infections and many abnormalities in pregnancy all carry an appreciable mortality, which could rise considerably if treatment was hampered by inadequate diagnosis. Furthermore, unexpected positive X-ray findings do occur, and one can never be quite sure that an X ray will not reveal an unsuspected lesion.

On the other hand, I suggest that many X rays of the coccyx and appendix, and some follow-through examinations after a barium meal might well be dispensed with. X-ray examination of the sacro-iliac joints is valuable if ankylosing spondylitis or infective arthritis is suspected, but it throws no light on sacro-iliac strain or disk lesions, and could perhaps be ordered less often in women. X ray of the lumbo-sacral spine should not be specified when lumbar spine only is meant.

Apart from restricting these few types of X ray, I feel that most practical benefit will come from improved techniques of radiography that reduce the gonad dose in each examination. These are being adopted, I think, by all radiologists, and I hope also by all non-radiologists who take X rays.

Yours, etc.,

F. M. HOOPER.

341A Anzac Parade,
Kingsford,
New South Wales.
December 20, 1957.

[1] *Brit. J. Radiol.*, 1955, 28: 266.

[2] "The Hazards to Man of Nuclear and Allied Radiations", 1956, H. M. Stationery Office, London.

[3] *Am. J. Obst. & Gynec.*, 1954, 67: 484.

[4] "Radiation Biology", 1954, edited by Hollaender, McGraw-Hill, Volume 1, Chapter 12, page 825.

THE PATIENT, THE SURGEON AND THE ANÆSTHETIST.

SIR: I would like to reassure Dr. Susman that the surgeon remains the leader of the surgical team.

However, he has overlooked the efforts made during the last decade, by the various Colleges of Surgeons and their associated faculties of anæsthesia, in promoting the art and science of anæsthesia. The specialist anæsthetist is now required to be skilled at all the techniques of his own speciality, and also to be proficient in pre-operative and post-operative care. A high standard of medicine is expected of him, especially with reference to the pulmonary and cardiac conditions. He must also be conversant with surgical techniques and problems.

The object of this increased responsibility was to enable the surgeon to lead a surgical team and cooperate with his colleague, the anæsthetist, in whom he could place complete confidence.

In the two cases quoted, surely the approach should have been: "What pre-operative care can we give to this patient in order to render him or her fit for anæsthesia?" Dr. Susman quotes one brief visit. In a team the surgeon and anæsthetist must visit a critically ill patient frequently in order to choose the optimum moment for operation.

With regard to the first case quoted, I would agree with the anæsthetists that to induce anæsthesia in a patient with a tension pneumothorax would be to court disaster. But relief of the pneumothorax, bronchoscopy under topical anæsthesia and aspiration of the affected lung might have markedly improved the condition of the patient.

Certainly many patients will improve under anæsthesia, but if their pre-operative condition is moribund, they will die rapidly when the anæsthetic is withdrawn.

There will be some cases when an anæsthetist will advise against operation. In a well-balanced team the surgeon will respect the advice of his colleague and cancel or defer the operation.

Yours, etc.,

E. R. REID.

Boulder City,
Western Australia,
January 8, 1958.

KURU.

SIR: I read with interest an article on kuru in a recent issue of this Journal by Zigas and Gajdusek.[1] Of particular interest is the similarity between the clinical picture described by these authors and that of neurolathyrism. Some of the features of human neurolathyrism are quoted verbatim from the excellent review on this subject by Selye:[2]

> Sometimes, there are prodromal sensory symptoms such as pain, prickling, numbness and cramps, but usually the patient suddenly feels weak, especially in the legs, and the muscles become tremulous when weight is put on them. Then, there is paresis of the legs, increased reflex irritability and, eventually, extreme spasticity and rigidity of the leg muscles. The gait becomes jerky, the steps short, and the patient tends to walk on the balls of the feet with the knees slightly flexed. Ankle clonus and adductor spasm of the thigh muscles develop easily, and therefore the patient walks jerkily and crosslegged. Often the walk is more like "waddling". In extreme cases, locomotion is only possible by crawling in a sitting posture. There may be no sensory disturbances or muscular atrophy, but frequently there is tingling, formication, lightning pains,

[1] M. J. AUSTRALIA, 1957, 2: 745.

[2] *Rev. canad. de biol.*, 1957, 16: 1.

diminution of tactile sensation, and complete loss of sensitivity to heat and pain with marked muscular wasting. The arms are much less frequently affected than the legs. The Babinski sign is present, and the deep reflexes are exaggerated. . . .

Experimental neurolathyrism has been induced in a wide variety of animals by the feeding of Lathyrus seeds or extracts. Such a condition is characterized by the presence of tremors, paralysis, etc., while the administration of a related compound iminodipropionitrile to rats has been shown to produce a choreiform syndrome (Selye[3]).

It is possible that the natives of the area under consideration have been eating various types of lathyrogenic grains. Such a possibility should at least be excluded in the investigation of this neurological condition, which is still of unknown ætiology.

Yours, etc.,

Department of Physiology, University of Adelaide, Adelaide.
COLIN J. SCHWARTZ.

December 24, 1957.

EYE INJURIES IN INDUSTRY: THEIR MANAGEMENT AND PREVENTION.

SIR: Much as I dislike disagreeing with my friend, Dr. Lennox Price, on the routine after-treatment of corneal foreign bodies (M. J. AUSTRALIA, November 23, 1957), I feel compelled to do so when his methods meet with the approval of Dr. Hugh G. Allen from the busy industrial centre of Newcastle (M. J. AUSTRALIA, December 14, 1957).

From the article of Dr. Lennox Price I gather that after the removal of every corneal foreign body a firm pad and bandage is applied and the eye inspected after 24 hours. This means that the worker will miss one, if not two, days' work. As many hundreds of these accidents occur daily throughout Australia, this means that the total loss of time would amount to one one-man-power year. Quite apart from the damage to vision and the all-too-frequent loss of an eye in the more serious accidents, the economic loss to employer and employee is by no means trivial.

At the request of the late Editor I wrote an article on "Injuries to the Eye in General Practice", which was published in the Journal of August 23, 1952. I then outlined a method of after-treatment of corneal foreign bodies which is routine with many industrial medical officers and ophthalmic surgeons. In most cases, after the instillation of a suitable ointment, the worker is instructed to return to work with the eye uncovered, but to report back within two days if the eye has not returned to normal within that time. In a long experience of industrial ophthalmology, I have seen no harm come from this method of treatment, and I do not appear to have lost the confidence of the worker or of his employer. Hence I must completely disagree with Dr. Lennox Price that this is "cavalier" treatment. Absenteeism is a serious problem in industry, not only for the employer, but for the worker, most of whom, for economic reasons, are only too anxious not to lose any time at work.

The importance of these injuries to the eye is out of all proportion to the size of the missile inflicting them. Apart from the loss of time caused by the minor accidents, too many eyes are still being lost or seriously damaged because the problem of prevention has not been seriously tackled. The prevalence of this type of injury reflects no credit on the practice of industrial opthalmology in this country. As an ophthalmic surgeon, I cannot recall with complacence a recent advertisement in this Journal of an ophthalmic practice for sale boasting of a return of £2000 *per annum* from "insurance work".

Yours, etc.,

33 Collins Street, Melbourne,
KEVIN O'DAY.

January 3, 1958.

PEPSINIZED GRASS POLLEN IN THE TREATMENT OF HAY FEVER: A FURTHER REPORT.

SIR: I have refrained from making comment of the paper by Colton and Robson in THE MEDICAL JOURNAL OF AUSTRALIA of September 7, 1957, concerning pepsinized grass pollen until such time as I could observe critically the result of our fourth season of full use of these substances in acute pollinosis. In this season, the mildest one for many years, we have treated 400 patients. It is known that at least half of these have had an adequate relief of symptoms and that not more than 40 have been referred to me as remaining in severe trouble. The usual standard has been applied, that if antihistamines give sufficient response we do not treat otherwise. We do not know what has happened to about one-half of the remainder, but they have had initial treatment with relief, and experience teaches us that most of these people come back if in trouble. At least 12 have come for their fourth season of treatment, 41 for their third and 69 for their second. So that at least one-fourth of the patients have found the treatment sufficiently satisfactory to give it a go for the second time.

Last season we treated 480; in 1955 about 450 in my absence. Most of the failures of 1955 and 1956, and quite a few of the successes, are now on pre-seasonal treatment, and considering the mildness of the season and the advent of the hydrocortisone snuffs, with their high level of publicity, the lesser number this year is not significant of a lack of public demand for this treatment by either laity or the general practitioners who refer the patients. This perhaps is a reasonable measure of whether it works or not.

It is regrettable that in sending this paper for publication, Professor Robson and Dr. Colton did not do me the courtesy of asking me to comment on it. I had had a short word in passing with Professor Robson, who told me of the result and that the verdict must be non-proven. We were both in haste and went our separate ways. But I think that it must also be appreciated that the negative is non-proven as well as the positive. The number treated is admitted to be statistically insignificant, and it quite apparently is so.

Dr. Clarke has already pointed out that the use of pethidine would invalidate a positive result, as it is a histamine liberator. Practically my only contact with the experiment was to advise a third member of the team against its use on these grounds. I suggested instead that distilled water *plus* air would produce an adequately similar weal by injecting it intradermally and there could not possibly be other than local effect. Incidentally, I may be old-fashioned, but I still shudder at the possible effect of giving even five minute doses of pethidine to a susceptible individual.

Allergic disease is psychosomatic, and it has always been in our minds on this matter that we might get our results by the fact of our trying to do something, that that something is visible, and that we have confidence in it. Others have suggested this, of course, and I am quite open-minded about it. But it has been a weakness of this second experiment that the personnel have all been trained to scepticism concerning immunological methods in allergic disease. One of them was a convinced sceptic because he had the experience of trying to help the failures of the 1955 season in my practice. It is admitted in this paper that the test was not a double-blind one, that the operators knew which was being given. Even with the best will in the world, the poker face is unattainable by all but a very few, and the bad results might as equally have been psychosomatically mediated as ours, but in the reverse direction. I think the psychosomatists must agree that there is this possibility.

Concerning the failures, it is a devastating experience to try to deal with a large number of these people, because they are pretty desperate, and I myself have been on the verge of throwing the treatment up completely in the mid-season of each year on account of these people. They are practically the only ones that I see nowadays, the treatment being carried on by my assistants and nurses. However, I make an annual review of the results and I talk to the people who have had the treatment afterwards, and I have no doubt that we must go on using it.

It is a further weakness of this experiment that no skin tests were done, as a clear-cut history was of sufficient value. This is not true, as many of the cases of apparent grass hay fever are really due to plantain pollen or to cladosporium allergy, and the grass plays a minor part only.

It is a regrettable fact that in a community where one in 13 are afflicted by spring pollinosis, and one in 1000 are so desperate with it as to seek specialist treatment in allergy clinics alone in each year, that departments of medicine are coloured by the nihilistic English concept of allergy. So that 7% of the population are labelled as respiratory neurotics or have some weird imbalance of the pituitary-adrenal axis, which almost certainly has no primary effect on the allergic reaction. This disease of spring pollinosis creates misery, inefficiency and impairment of domestic and personal relations for at least 1% of the

people of South Australia and Victoria for four months of the year. It increases as the imported pasture grasses replace the harmless native ones. Surely it is time that it received official recognition as a serious health and economic problem, and that the task of combating it were taken off the hands of the small body of allergists, kept too busy by it to maintain any aggressive research.

Five or six years ago an eminent visiting Scottish physician said in a lecture that the antihistamines had solved the problem of hay fever. How right he was, any doctor who deals with the people knows. When I was in London in 1955 the Fellowship of Medicine could send me to only two places worth visiting as being interested in asthma and allergy. In Sydney in August for the allergists' annual meeting we were taken to a lunch-hour meeting at the Royal Prince Alfred Hospital, where asthma was to be discussed. Fully competent physicians there decried the immunological nexus of allergy and produced the old story of injections with sterile water; but they did not explain why, if they get as good a result with sterile water as the allergist gets with his extracts, they did not go on treating asthmas with sterile water, for the allergist undoubtedly gets results in the suppression of allergic disease that the general physician does not, unless he uses the steroids improperly.

The current teaching in all our medical schools is the British teaching: psychosomatism, pituitary-adrenal axis and chronic bronchitis. It is effectual to the point that there are at least 5000 asthmatic cripples in Australia and another 50,000 whose lives are spoilt by their suffering from that disease, and second-year registrars at the Royal Adelaide Hospital do not know how to handle the asthmatic who has broken out of prednisone control. I know that the allergists have not produced the whole answer to allergic disease, nor have they produced a credible concept of the allergic state that can be lined up with the principles of pathology. But then the general physician and other internal specialists have not produced the whole answer to hypertension or duodenal ulcer and a thousand other things, and they still theorize about the mechanism of production. I am not a true allergist, but a physician, who, fascinated by the mystery of allergy, does his best about it and uses the allergic method, and is critically satisfied that in an imperfect world he is helping these unfortunates as he could not help them without it, and to a degree which is favourably and strictly comparable with the results obtained by the internists in other diseases, except through the help of the antibiotics in infection. May I enter this plea, that the physicians who will not accept allergy, open their minds and give proper and critical thoughts to this very real and urgent problem of doing something about allergic disease.

Yours, etc.,

163 North Terrace,
Adelaide,
December 19, 1957.

CYRIL T. PIPER.

Obituary.

MICHAEL RICHARD FLYNN.

WE are indebted to Dr. Harry Daly for the following appreciation of the late Dr. Richard Flynn.

Richard Flynn died from a cerebral tumour on December 11, 1957, at the age of 64 years.

I first met Dick Flynn as a painstaking demonstrator in zoology, ever ready to answer the simplest question from students and to appreciate their difficulties. His father, John Flynn, M.D., an Irish graduate, came to Australia in 1888, and married Maud Witton, daughter of Richard Witton, a Monaro pastoralist, whose father had left England to take up land under the Peel Scheme for colonizing Swan River, arriving in Western Australia on May 8, 1830, on the *James*.

Richard Flynn was the eldest of a family of nine, six sons and three daughters; all six sons graduated in medicine at the University of Sydney. He matriculated from Marist Brothers' High School, Sydney, and after graduating bachelor of arts he entered medicine and science. He graduated splendidly in science (B.Sc.) with double first-class honours in physiology and zoology, being awarded Professor Haswell's Prize in zoology. His career in medicine was no less distinguished. He won the John Harris Scholarship for anatomy and physiology, the Clipsham Memorial Prize for operative surgery, and Professor Sandes's prize for surgery, and was awarded first-class honours at graduation. He was appointed, on graduation, resident medical officer at Royal Prince Alfred Hospital, where we served a term together.

After his residency at Royal Prince Alfred Hospital he was awarded the Walter and Eliza Hall Travelling Medical Fellowship, and went to England. He resigned this Fellowship to become a Fellow in Surgery at the Mayo Clinic, United States of America, where he remained for three and a half years. He was granted the degree of master of surgery (University of Minnesota, United States of America) in 1924, being the first Australian medical graduate on the staff of the Mayo Clinic.

On returning to Sydney, he gained appointment to the surgical staff of Royal Prince Alfred Hospital and Lewisham Hospital. In due course he became the senior surgeon at both hospitals, and later was appointed consulting surgeon at each. He was made a Fellow of the Royal Australasian College of Surgeons in 1929 and gained the degree of doctor of medicine (Sydney) in 1931. His surgical ability and qualifications were such that he took the place of the Professor of Surgery, Professor Harold Dew, when the latter was abroad in 1953. He also had a long association with the faculty of dentistry, being lecturer in surgery and consulting surgeon to the Dental Hospital of New South Wales.

As both student and doctor, Richard Flynn found time for many other activities associated with his student and professional life. With tireless energy, he took an active part in university life—as president of the Medical Society, director of the Union and president of the Athletic Club, and he served on the committee of the Undergraduates' Association, the Sports Union, the Swimming Club, the Arts Society and the Science Society. He was elected president of the Standing Committee of Convocation, University of Sydney, for two terms. In addition he contributed over a hundred articles to numerous medical publications.

Until within a short time of the onset of his fatal illness, Dick Flynn was blessed with great good health, and never spared himself in his devotion to those who sought his aid. He will long be remembered with grateful affection by his many friends, patients and students as a man who shone quietly in a room, who met you with a warm handshake, a few words that were sincere and a smile you carried in your memory. We offer our deepest sympathy in her sad loss to his widow, Roma, who over many years was his constant companion and helpmate.

LEONARD JAMES PELLEW.

We are indebted to Dr. A. R. Southwood for the following appreciation of the late Dr. Leonard James Pellew.

Dr. Leonard James Pellew, who practised in Adelaide for forty years, died at a private hospital there on November 3, 1957. He was aged 77 years.

Leonard James Pellew graduated M.B., B.S. at the University of Adelaide in 1906. He entered general practice in the country in South Australia, first at Balaklava. In 1913 he took over the practice of Dr. J. Riddell at Port Augusta. At that time the transcontinental railway line to Kalgoorlie was under construction, and additional duties fell to the Port Augusta doctor. Work at the Government hospital in the town was heavy. Pellew was instrumental in having the institution graded as a training school for nurses; he devoted himself enthusiastically to that work.

On the outbreak of the first World War in 1914, Leonard Pellew applied for a post in the Royal Army Medical Corps, hoping by that means to move overseas without delay. The introduction of the scheme for enlisting Australian doctors in the Royal Army Medical Corps enabled him to achieve that aim. With his wife and young family, he left for England by regular mail boat early in 1915. He was soon posted to the staff of the 21st Casualty Clearing Station in France, and attained his desire to undertake war surgery; in the unit he was associated with Dr. Gordon Bell, who later became Professor of Surgery in the Otago Medical School. Pellew had for several years taken special interest in general surgery, and during his term of country work had developed sound surgical technique. His diagnostic acumen was of high order, and he became recognized as a capable surgeon. He was mentioned in dispatches for his work on service.

He returned to Australia in 1917, at the end of his period of service with the Royal Army Medical Corps. He still had the responsibility of the Port Augusta practice; he decided to dispose of that and to re-enlist. Delay in the transaction for sale of the practice irritated him; by the time arrangements for transfer were completed the war was nearing its end; he re-enlisted, then in the Medical Corps of the Australian Imperial Force, but the war ended before he could be drafted overseas again. Pellew also sought enlistment in 1939, but his age precluded him from service overseas. For many months he assisted the recruiting campaign by giving a series of lectures throughout South Australia, and he was a medical examiner.

At the end of 1918 Pellew entered practice in Adelaide. He took over the consulting rooms and home of Dr. Charles Todd, a prominent Adelaide surgeon, who had died just before. The premises were in a central position in the city, fronting Victoria Square and a few yards from the General Post Office. He joined Dr. Herbert Letcher in a busy practice, Pellew devoting himself mainly to the surgical work. Later he was associated with Dr. Sydney Dawkins. He remained in active practice in Adelaide until the recent winter. He was president of the South Australia Football League and took a keen interest in the league matches. It was while leaving the official box at the Adelaide Oval in June, 1957, that he slipped on the stairway and fractured a femur. For a man previously so active, he bore the several months of enforced rest with reasonable equanimity. He was just resuming his consulting work when the final illness came.

Pellew did not seek higher academic qualifications or honorary posts in public hospitals. For most of the time in Adelaide he was official surgeon to the South Australia Fire Brigades Board, as well as to several league football teams. The busy work of his surgical practice and his numerous duties with public bodies and charitable institutions left him little spare time. He spent a year in post-graduate studies in England and the United States in 1926, and made short visits to Japan and other countries of the East. Pellew made a special hobby of the study of history. His general knowledge was both wide and deep, and such was his facility of expression that his services as a lecturer were in great demand by many organizations throughout South Australia. He was a busy doctor all through his professional life. He was the friend, medical adviser and accepted confidant of hosts of people covering a broad social spectrum.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED DECEMBER 28, 1957.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.[2]	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.[3]
Acute Rheumatism	..	2(2)	1	..	2	..	..	..	5
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	2	..	..	..	..	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	12(8)	10(7)	3(3)	..	1	..	..	2	28
Diphtheria	1(1)	..	2(1)	..	..	..	..	..	3
Dysentery (Bacillary)	..	..	2(1)	..	..	..	2	..	4
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	22(14)	3(1)	..	..	32(2)	..	..	..	57
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	1	..	1
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	..	..	..	..	..	..	1	1	2
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	..	..	..	..	..	..	..
Puerperal Fever	..	1	..	..	1(1)	..	..	..	2
Rubella	..	18(13)	5(4)	..	25(21)	..	..	..	48
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	5(3)	14(5)	2(1)	..	2(1)	..	..	..	23
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	1	..	..	..	2
Trachoma	..	..	..	..	4	..	..	..	4
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	22(10)	6(3)	..	..	2(1)	..	..	..	30
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from South Australia.

people of South Australia and Victoria for four months of the year. It increases as the imported pasture grasses replace the harmless native ones. Surely it is time that it received official recognition as a serious health and economic problem, and that the task of combating it were taken off the hands of the small body of allergists, kept too busy by it to maintain any aggressive research.

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At the end of 1918 Pellew entered practice in Adelaide. He took over the consulting rooms and home of Dr. Charles Todd, a prominent Adelaide surgeon, who had died just before. The premises were in a central position in the city, fronting Victoria Square and a few yards from the General Post Office. He joined Dr. Herbert Letcher in a busy practice, Pellew devoting himself mainly to the surgical work. Later he was associated with Dr. Sydney Dawkins. He remained in active practice in Adelaide until the recent winter. He was president of the South Australia Football League and took a keen interest in the league matches. It was while leaving the official box at the Adelaide Oval in June, 1957, that he slipped on the stairway and fractured a femur. For a man previously so active, he bore the several months of enforced rest with reasonable equanimity. He was just resuming his consulting work when the final illness came.

Pellew did not seek higher academic qualifications or honorary posts in public hospitals. For most of the time in Adelaide he was official surgeon to the South Australia Fire Brigades Board, as well as to several league football teams. The busy work of his surgical practice and his numerous duties with public bodies and charitable institutions left him little spare time. He spent a year in post-graduate studies in England and the United States in 1926, and made short visits to Japan and other countries of the East. Pellew made a special hobby of the study of history. His general knowledge was both wide and deep, and such was his facility of expression that his services as a lecturer were in great demand by many organizations throughout South Australia. He was a busy doctor all through his professional life. He was the friend, medical adviser and accepted confidant of hosts of people covering a broad social spectrum.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED DECEMBER 28, 1957.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.[2]	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.[3]
Acute Rheumatism	..	2(2)	1	..	2	..	..	..	5
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	2	..	..	..	..	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	12(8)	10(7)	3(3)	..	1	..	..	2	28
Diphtheria	1(1)	..	2(1)	..	..	..	..	..	3
Dysentery (Bacillary)	..	..	2(1)	..	..	..	2	..	4
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	22(14)	3(1)	..	..	32(2)	..	..	..	57
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	1	..	1
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	..	..	..	..	..	..	1	1	2
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	1	..	..	..	..	..	..
Puerperal Fever	..	..	1	..	1(1)	..	..	..	2
Rubella	..	18(13)	5(4)	..	25(21)	..	..	..	48
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	5(3)	14(5)	2(1)	..	2(1)	..	..	..	23
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	1	..	..	..	2
Trachoma	..	..	..	..	4	..	..	..	4
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	22(10)	6(3)	..	..	2(1)	..	..	..	30
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

[2] Figures not available.

[3] Figures incomplete owing to absence of returns from South Australia.

In recognition of his public service he was made a Commander in the Order of the British Empire in the 1957 Birthday Honours. Leonard Pellew married Miss Hirell Ternouth, of Semaphore. He is survived by her and their three children. Miss Jane Pellew, B.D.S., Mr. L. J. T. Pellew, F.R.C.S., and Dr. R. A. A. Pellew, M.R.C.P., F.R.A.C.P., are all in professional practice in Adelaide.

Research.

PFIZER FELLOWSHIP.

THE selection committee for the Pfizer Fellowship for Research (Overseas) in Clinical Medicine, comprising the Professors of Medicine of all Australian University Medical Schools, has awarded the Fellowship for 1958 to Dr. Barry G. Firkin. Dr. Firkin has been for some years working at the Clinical Research Unit, Royal Prince Alfred Hospital.

Congresses.

AUSTRALASIAN CONFERENCE IN RADIATION BIOLOGY.

THE second Australasian Conference in Radiation Biology will be held at the Cancer Institute, Melbourne, Australia, during the week December 15 to 19, 1958. Proffered papers on relevant subjects are invited, and titles and a 250-word abstract should be in the hands of the convener by July 31, 1958. Further information for those wishing to attend or present papers may be obtained from the convener, Dr. J. H. Martin, Physics Department, Cancer Institute Board, 483 Little Lonsdale Street, Melbourne, Victoria, Australia.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Haber, Richard William, M.B., B.S., 1957 (Univ. Sydney), 2B Tusculum Street, Potts Point, New South Wales.

Petersons, Valdemars Vladislavs, M.D., 1943 (Univ. Riga), registered in accordance with the provisions of Section 17 (1) (*c*) of the *Medical Practitioners Act*, 1938-1957, 25 Dowding Street, Panania, New South Wales.

Deaths.

THE following deaths have been announced:

RANDALL.—Clement William Randall, of Sydney, at Tenterfield, New South Wales.

GILL.—Leslie Pejasch Gill, on January 12, 1958, at Melbourne.

MCLACHLAN.—Duncan McLachlan, on January 14, 1958, at Parramatta.

Medical Appointments.

Dr. T. W. Murray has been appointed senior medical officer in the Mental Hygiene Branch, Department of Health, Victoria.

Dr. J. L. Evans has been appointed psychiatrist in the Mental Hygiene Branch, Department of Health, Victoria, and Deputy Superintendent of the Mental Hospital, Larundel, Victoria.

Dr. A. S. Ellis has been appointed Psychiatrist Superintendent in the Mental Hygiene Branch, Department of Health, Victoria, and Superintendent of the Mental Hospitals, Ararat and Warrnambool, Victoria.

Dr. F. W. Lustig has been appointed medical officer in the Mental Hygiene Branch, Department of Health, Victoria.

Diary for the Month.

FEB. 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
FEB. 5.—Western Australian Branch, B.M.A.: Branch Council.
FEB. 6.—South Australian Branch, B.M.A.: Branch Council Meeting.
FEB. 7.—Queensland Branch, B.M.A.: General Meeting.
FEB. 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales. Anti-Tuberculosis Association of New South Wales.

Queensland Branch (Honorary Secretary, 88 L'Estrange Terrace, Kelvin Grove, Brisbane, W.1): All applicants for Queensland State Government Insurance Office positions are advised to communicate with the Honorary Secretary of the Branch before accepting posts.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

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